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# Stress reactivity, stress appraisal and coping responses in schizophrenia

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# STRESS REACTIVITY, STRESS APPRAISAL AND COPING RESPONSES IN SCHIZOPHRENIA

by

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ABSTRACT OF THE DISSERTATION

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Psychosocial factors have long been recognized as important to the etiology of schizophrenia. According to the stress-vulnerability model, the experience of stress is critical to the onset and/or maintenance of schizophrenia. Although there is no conclusive evidence to suggest that people with schizophrenia experience more stressful events than the general population, there is ample evidence that stress is linked with the course of illness. Traditionally, two lines of research have examined stress processing mechanisms: one focusing on the biological response to stress by studying the hypothalamic-pituitary-adrenal (HPA) axis and the other focusing on the psychological mechanisms delineated in the transactional stress model. According to the transactional stress model, an individual's reaction to stressors is determined, in part, by his or her appraisal of the stressor. The impact of a stressor is also determined by one's ability to cope with the situation, which in turn is related to the availability of various coping resources. Previous studies show that individuals with schizophrenia tend to use maladaptive coping strategies when faced with stressors. Research has also documented a disruption in their

HPA axis function. The interactions of these processes, however, have not been explicitly investigated in schizophrenia. This study explored the relationships among appraisal, coping strategies, cortisol secretion and perceived stress in a group of individuals with schizophrenia, their genetic high-risk siblings and community controls. The study evaluated participants' appraisals and coping strategies to experimentally induced conditions of stress as well as their usual coping strategies to everyday stressors. Coping resources, such as social support and cognitive ability, were tested as mediators for group differences in perceived stress and use of different coping strategies.

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## Chapter 1: Introduction and Overview

According to the stress-vulnerability model, the experience of stress is critical to the onset and/or maintenance of schizophrenia (Zubin & Spring, 1977). Research supports the notion that individuals with schizophrenia experience more stress than healthy individuals, although studies that have examined the relationship between stress and psychosis have produced mixed results. For example, some studies report an increase in the number of life events experienced prior to the onset of an acute psychotic episode (Bebbington et al., 1993; Brown & Birley, 1968; Canton & Fraccon, 1985; Chaven & Kulhara, 1988; Day et al., 1987; Mazure et al., 1997; Michaux et al., 1967; Scwartz & Myers, 1977) but others have not (Chung et al., 1986; Gruen & Baron, 1984). Thus, there is no conclusive evidence to suggest that people with schizophrenia experience more stressful events than the general population, although there is ample evidence that stress is linked with the course of illness (Walker et al., 2008). One central limitation of this body of literature is the reliance on the experience of *major* life events as a measure of the experience of stress. Research in the general stress literature highlights the importance of measuring other types of stressors (i.e., daily hassles) as well as qualitative appraisals to these stressors in order to fully understand the relationship between stressful experiences and mental health outcomes.

Research among community samples has documented that differences in the appraisal of specific events (i.e., whether events are perceived as threats or challenges) are related to different outcomes and may result in more perceived stress. In other words, individuals who perceive an event as a threat, rather than a challenge, are more likely to perceive that event as stressful. There have been no investigations of event appraisals

among individuals with schizophrenia, and it is unclear whether these individuals experience more stress, at least in part, because they are more likely to appraise situations as threats. There is some research that suggests that individuals with schizophrenia use less effective coping strategies compared to community controls (Horan et al., 2007; Ritsner et al., 2006), but it not known whether reliance on these strategies is related to their appraisals of such events or to a lack of effective coping resources such as social support and problem solving skills.

Another line of research in understanding the role of stress has investigated the biological stress response system in individuals with schizophrenia. Such investigations have mainly focused on cortisol, a hormone released by the adrenal glands in response to stress. A majority of studies have found higher baseline levels of cortisol in individuals with schizophrenia compared with healthy controls [see (Walker & Diforio, 1997) for a review] suggesting a disruption of the stress regulating system in schizophrenia. High cortisol levels in schizophrenia could be a consequence of the stress of experiencing psychotic symptoms. However, there is evidence that cortisol levels are significantly higher in individuals with schizophrenia immediately prior to the onset of psychotic episodes as compared to periods of recovery (Walker & Diforio, 1997), suggesting that higher cortisol levels are not solely related to the psychotic symptoms. Basal cortisol levels have also found to be higher in individuals with schizotypal personality disorder (Walker et al., 2001), a disorder thought to be genetically related to schizophrenia (Cadenhead, 2002), than in age-matched controls.

To date, research on the role of stress in schizophrenia has documented that individuals with schizophrenia experience more stress, although they do not necessarily

report more stressful life events. Further, there is some evidence that individuals with schizophrenia experience a disruption in the biological system that responds to stress. There is also some evidence that individuals with schizophrenia are more likely to use ineffective coping strategies to alleviate stress. However, there has been no systematic investigation of how life events, appraisals of these events, perceived stress, coping strategies, and the biological stress response system interact to increase the subjective experience of stress in individuals with schizophrenia. A better understanding of the mechanisms by which an event is experienced as a stressor in individuals with schizophrenia could further our understanding of the role of stress in triggering relapse of psychotic episodes. There is a dearth of literature on stress processing in individuals at high-risk for schizophrenia. Studying these mechanisms in a genetic high-risk group has the potential to inform us about the role of the genetic liability towards schizophrenia in biological and psychological stress processing systems. Results of this research may also provide a basis for the development of interventions targeted at stress management to prevent or delay stress-related relapse.

This study was a two-pronged investigation of the relationships among objective life stress, perceived stress, biological response to stress, cognitive appraisal, coping skills, and coping resources in individuals with schizophrenia, full biological siblings of individuals with schizophrenia, and community controls. One part assessed similarities and differences in reported life stress (life events and daily hassles) as well as coping strategies and coping resources. This approach was more ecologically valid as it taps into the actual experiences of stress in daily life, although there can be no control over the types of stressors participants will experience. The second part of the study examined if

and how the three groups will differ from each other in their biological and psychological reactions to laboratory induced stress. This more controlled, experimental approach allowed for a systematic investigation of group differences in stress responses to the same event.

## Chapter 2: Literature Review

Psychosocial factors have long been recognized as important to the etiology of schizophrenia (Gottesman, 1991). The specific environmental contributions to the onset and/or maintenance of this disorder have been elusive and are generally termed *stress*. Although the mechanism by which stress interacts with the genetic liability for schizophrenia is not yet known, the leading conceptual model presumes that an "excessive level of stress" is one circumstance under which genetic vulnerability can express itself in the form of schizophrenia (Phillips et al., 2006b). Stress can be broadly defined as a person-environment interaction that is perceived by the person as taxing or exceeding his or her resources (Lazarus & Folkman, 1984) and involves a complex interaction of psychological and physiological processes. In the section that follows, literature in the following areas will be reviewed: stress in schizophrenia, models of stress, interrelations among stress, appraisal, and coping, and social support.

### *Stress and schizophrenia*

Measurement of life events using retrospective interviews has been a common approach to measuring stress in schizophrenia. However, the results of such retrospective studies have been mixed. One of the first quantitative studies to examine the interaction of the experience of stress and the course of psychosis was conducted by Brown and

Birley (1968). They reported that those with an established diagnosis of schizophrenia experienced twice the number of life events during the three-month period before hospitalization compared to an age-matched sample of community controls. Their sample consisted of both first episode and relapsing patients, and they found that forty-six percent of patients reported an independent life event (i.e., an event unlikely to be caused by symptoms) in the three-week period before a psychotic episode compared with only fourteen percent of the community sample. Except for this three-week period prior to an episode, life event rates for the two groups did not differ significantly. Some subsequent studies have also reported increased number of life events experienced prior to the onset of an acute psychotic episode in relapsing patients (Bebbington et al., 1993; Canton & Fraccon, 1985; Chaven & Kulhara, 1988; Day et al., 1987; Mazure et al., 1997; Michaux et al., 1967; Scwartz & Myers, 1977) but others have not (Chung et al., 1986; Gruen & Baron, 1984). There is also limited evidence for increased frequency of life events among first episode patients. For example, Jacobs and Meyers (1976) reported that newly diagnosed schizophrenia patients experienced more life events in the year prior to hospitalization than a healthy control group in a comparison year. However, this difference was only significant when dependent events were considered. Several factors may account for the discrepant results, including time interval under study (e.g., three weeks versus one year), diagnostic criteria used to identify patient samples, and match criteria for patient and control samples (Neale & Oltmanns, 1980). In a study of individuals with genetic high-risk for schizophrenia, Miller and colleagues (2001) reported no differences in the number of life events experienced by the high-risk group compared to community controls or first-episode psychosis patients.

Longitudinal investigations of the relationship between the experience of stressful events and relapse of illness have also produced mixed results. For example, Ventura and colleagues (Ventura et al., 1989) interviewed 30 outpatients with schizophrenia on a monthly basis for one year and found a significantly higher number of independent life events in the month preceding symptom exacerbation. Pallanti et al. (1997) reported results similar to Ventura, but another study failed to replicate this pattern (Hirsch et al., 1996), perhaps due to differences in their definitions of relapse.

The retrospective and longitudinal studies described above examined a range of life events, which could vary from individual to individual. In contrast, there have been a number of quasi-experimental studies in which all participants were exposed to the same life event. A few early studies reported increased incidences of schizophrenia among military recruits exposed to extreme combat display (Paster, 1948; Steinberg & Durrell, 1968; Wagner, 1946). More recent studies have suggested that although the experience of psychotic symptoms after such exposure might be more common, the onset of psychotic disorders after exposure to warfare is rare (Beighley et al., 1992; Tennant, 1985).

Migration is another commonly studied life event in relation to schizophrenia and provides the most compelling evidence for the relationship between life stress and schizophrenic illness. In a meta-analysis of 18 studies, Cantor-Graae and Selten (2005) reported a mean weighted effect size of 2.9 for the risk of developing schizophrenia among first and second generation migrants. Significant heterogeneity was found across studies indicating that different migrant groups cannot be regarded as coming from a homogenous population. However, the relative magnitude of this effect size argues for a strong association between migration and schizophrenia. Although the mechanism

through which migration can impact the development of a psychotic disorder remains to be studied, it is likely that migration confers an ethnic disadvantage. Being part of a minority group may result in a chronic stressful experience, which in turn may contribute to the onset or relapse of psychosis.

Variability in the results of the above reviewed life event studies suggests that other factors likely contribute to the relationship between stressful experiences and the development of psychosis. One fundamental drawback of the life events approach is that it fails to consider the effects of mediating factors such as desirability, predictability and perceived control over events (Phillips et al., 2007). Another major criticism is that it doesn't consider differences among individuals in their reactions to stressful events. For example, certain minor interpersonal events, such as rudeness on the part of a stranger, can be highly stressful to some, and not even be consciously processed by others (Walker et al., 2008). In addition, major life event checklists often do not account for stressful experiences resulting from day-to-day living, experiences which are often referred to as daily hassles.

In recognition of some of the limitations of the life events approach, a few studies have assessed the impact of *minor* events or hassles on the course of schizophrenia. These are generally assessed using questionnaires which ask about participant's day-to-day stressors related to weather, traffic, childcare, spousal relations, etc. In a retrospective investigation, Norman and Malla (1991) studied the relationship between perceived stress and major as well as minor events. They administered self-report measures of major life events, daily hassles and perceived stress to ninety-five patients diagnosed with DSM-III-R schizophrenia. They found that total number of daily hassles over the past month were

more predictive of perceived stress than total number of major life events over the past month. In a subsequent report, these researchers reported significant correlations between daily hassles occurring in the previous month and positive symptoms in twenty-five percent of their patient sample (Norman & Malla, 1994).

Myin-Germeys and colleagues used the experience sampling method as an alternative approach to assess the experience and impact of day-to-day stressors and psychotic symptoms. These researchers recruited individuals with psychosis, their first-degree relatives, and community controls and asked them to record their activities, thoughts, mood, and appraisals of the current situation at ten random time points over six consecutive days. They found no differences between relatives and controls in the number of stressful events reported but the patient group reported more minor stressful events, especially those related to social situations. The authors also reported a positive correlation between perceived stress and negative affect, which was strongest in the patient group (Myin-Germeys et al., 2001). A potential confound of this study is that patients might encounter different events than their asymptomatic relatives or community controls. For example, many individuals with schizophrenia are unemployed and may spend much of their time in day treatment programs. They probably interact with other individuals with schizophrenia and/or with medical staff more frequently than their asymptomatic relatives. Thus, it is unclear whether patients report more stressful events because of differences in environment or social circumstances (e.g., smaller social networks, low social support) or because they are more likely to perceive benign or neutral events as stressful. Although studying life stress through questionnaires and experience sampling methodology provides ecological validity, experimental methods

where all participants are exposed to the same stressor can add to our knowledge about how individuals with schizophrenia differ in their reactions to the same stressor.

***Models of stress***

According to Walker and colleagues (2008), an experience can only be considered stressful if it elicits a biological response that affects the brain. A commonly studied stress-response system is the hypothalamic-pituitary-adrenal (HPA) axis. This system governs a complex cascade of hormonal events and has been linked with a range of mental disorders, including psychosis (Walker et al., 2008). In response to stress, the periventricular nucleus of the hypothalamus releases corticotrophin releasing hormone (CRH), which triggers the pituitary gland to secrete adrenocorticotropic hormone (ACTH). This in turn leads to the secretion of cortisol from the adrenal glands (Corcoran et al., 2003). Since cortisol is the end product of the HPA axis and can be easily assayed in saliva, it is generally used in research as a measure of HPA axis function.

Typically, cortisol, as well as other indices of the HPA axis, follow a circadian rhythm. Cortisol levels are at their lowest at night, just after the onset of sleep. Cortisol levels begin to rise soon before an individual wakes up and reach their peak during early morning hours; they gradually decline during the day (Walker et al., 2008). Individual differences in HPA activity can be accounted for by genetics (Bartels et al., 2003), diet, and amount of exercise (Kanaley et al., 2001). Sex differences in HPA responses have also been studied, with consistent evidence for adult women showing lower HPA activity than men of the same age (Kajantie & Phillips, 2006). In individuals with schizophrenia, elevated baseline levels of cortisol have been reported (Walker & Diforio, 1997; Walker et al., 2008). There is also evidence that individuals with schizophrenia who are being

treated with neuroleptics show a blunted cortisol response to a series of laboratory stressors, including surgical procedures, mental arithmetic, and cold pressor test (Gispen-de Wied, 2000).

One group of researchers has investigated cortisol reactivity specifically to psychosocial stressors and also reported a blunted cortisol response. Jansen and colleagues (1998) compared 10 males with schizophrenia to 10 healthy males in their responses to a public-speaking task. They reported that the stressor increased heart rate in both patients and controls to the same degree but did not result in increased salivary cortisol in patients as it did for controls. They later replicated this finding in a larger sample (18 patients with schizophrenia and 21 controls) in a study of HPA activity in response to both a physical and psychosocial stressor. The physical challenge consisted of ten minutes of exercise on a stationary bicycle, and the psychosocial stressor was a ten-minute public speaking task. There was no difference in cortisol reactivity between patients and controls during the physical stressor but individuals with schizophrenia showed a significantly lower cortisol response to psychosocial stress, compared to healthy controls (Jansen et al., 2000b). Cortisol reactivity has not explicitly studied in individuals at genetic high-risk for developing schizophrenia. In a study of children with Multiple Complex Developmental Disorder, a disorder in which a subset develop schizophrenia in adulthood, Jansen and colleagues (2000a) reported a decreased HPA response to psychosocial stress. It has been hypothesized that patients with schizophrenia are not able to appropriately respond to some stressors because they have difficulty interpreting its' context (Gispen-de Wied & Jansen, 2002).

It is important to consider the context in which a stressor occurs because stress is not necessarily a unitary phenomenon and should be studied as a multidimensional construct (Jones & Fernyhough, 2007). Therefore, in understanding an individual's physiological reaction to a stressor, that individual's perception of the situation should also be considered. According to the transactional stress model, an individual's reaction to stressors is determined, in part, by his/her appraisal of the stressor. The impact of a stressor is also determined by one's ability to cope with the situation, which in turn is related to the availability of various coping resources (Hobfoll, 1989; Lazarus & Folkman, 1984).

Appraisal specifically refers to the perception, interpretation, and evaluation of a stressor. It is divided into two processes: primary appraisal and secondary appraisal. Primary appraisal is the perception of the nature and degree of risk and secondary appraisal is the perception of resources or abilities to cope with the stressor. According to the model, primary appraisals are further divided into "threat" and "challenge" evaluations. A threat appraisal anticipates harms or losses and is characterized by negative emotions such as fear, anxiety, and anger. Challenge appraisals focus on the potential for growth or gain and call for mobilization of coping efforts. They are characterized by positive emotions, such as excitement and eagerness (Lazarus & Folkman, 1984). Coping is defined as one's cognitive and behavioral effort to manage the demands of a stressful situation. Coping behavior can be divided into many different styles. For example, one can engage in task-, emotion-, approach-, or avoidance-oriented coping. Task-oriented or problem-focused coping is used to actively solve a problem, perhaps by cognitive re-conceptualization, and potentially minimize its adverse effects.

Emotion-oriented coping strategies tend to be person-oriented and may involve emotional responses such as self-preoccupation and self-blame. Approach- and avoidance-oriented coping styles are more general terms and do not distinguish between task- versus person-oriented approaches. Approach-related coping is generally conceptualized as any cognitive and behavioral attempts at resolving the conflict situation, whereas avoidance-oriented coping involves minimizing the importance of, or avoiding the stressful situation by self-distraction, denial, or engagement in a substitute task (Ritsner et al., 2006; Ventura et al., 2004).

***Stress, appraisal, coping, and social support***

In the general population, the magnitude of the physiological stress response is related to appraisal of the stressor as threatening or challenging (Peters et al., 1998; Tomaka et al., 1993). In a student sample, Nicholson (1992) demonstrated that a threat appraisal of an exam was strongly positively correlated with salivary cortisol before the exam and a challenge appraisal was strongly inversely correlated with cortisol secretion. Threat appraisals were also positively correlated with subjective stress in another study (Tomaka et al., 1993). In a recent investigation, Gaab and colleagues (2005) demonstrated that anticipatory appraisals of a public speaking task were predictive of cortisol responses during the stressor, providing further evidence that the magnitude of the biological response to stress is determined, in part, by psychological factors. This relationship has not been explicitly studied in individuals with schizophrenia, who are known to have differences in their biological stress-response system.

In addition to abnormalities in the HPA axis, there is some evidence that individuals with schizophrenia tend to use maladaptive coping strategies. Research in

several control and clinical populations, including patients with alcoholism, depression, cancer, chronic pain, and AIDS, has noted that approach coping is associated with favorable outcomes whereas use of avoidance coping is thought to contribute to worse outcomes (Moos, 1993, 2002). Individuals with schizophrenia are noted to be more likely to use avoidance or emotion related coping strategies, although most of the research on coping behavior has focused on dealing with psychotic symptoms rather than life events or daily hassles (Carter et al., 1996; Wiedl & Schottner, 1991). However, a number of investigations have examined coping responses to life stress and found that individuals with schizophrenia use avoidance as a frequent coping response (Hultman et al., 1997; Jansen et al., 1999; Jansen et al., 1998). In a prospective study of 42 consecutively admitted inpatients with schizophrenia, Hultman (1997) found that withdrawal was the most commonly used coping strategy when faced with life events. Ventura and colleagues (2004) compared 29 patients with schizophrenia to 24 controls on their coping styles to one negative interpersonal life event using the Coping Responses Inventory. Individuals with schizophrenia were found to be significantly less likely than controls to use approach related coping responses.

As discussed above, studies using life-event methodologies are subject to criticism on the basis that between-group differences might simply reflect differences in the types of stressful events encountered by the groups. Using a quasi-experimental design, Horan et al (2007) studied stress and coping related to an earthquake that hit southern California in 1994. They found that individuals with schizophrenia reported less use of approach coping as compared to healthy controls as well as individuals diagnosed with bipolar disorder. In a study of coping related to experimental stressors, Horan and

Blanchard (2003) again reported more common use of maladaptive coping strategies by individuals with schizophrenia.

Studies of coping behavior in schizophrenia have revealed that coping style might be related to various psychological and cognitive factors. For example, among individuals with schizophrenia, high self-efficacy (operationally defined as high self-esteem, self-report of positive coping with stressful events and perceived social support) is significantly positively correlated with approach coping (Ventura et al., 2004). The same study also reported that better performance on a measure of sustained attention was associated with more frequent use of approach coping. Coping styles have been reported to be related to negative mood (Horan & Blanchard, 2003).

Coping styles can also have an impact on the physiological stress response. In their review of the stress literature, Olff et al. (2005) found that coping styles based on high levels of avoidance and denial have been associated with increased neuroendocrine activity (i.e., more pronounced and prolonged neuroendocrine stress reaction), whereas coping styles characterized by active, direct, and problem-focused strategies have been associated with reduced neuroendocrine reactivity. These associations between coping style and the HPA axis have not been explicitly investigated in individuals with schizophrenia.

Coping styles, in part, can be influenced by the availability of coping resources (Lazarus & Folkman, 1984). One such resource is social support. Social support can be defined as “the perception or experience that one is loved and cared for by others, esteemed and valued, and part of a social network of mutual assistance and obligations” (Wills, 1991). In a recent review, Taylor (2007) reported that research has consistently

demonstrated the effect of social support on the reduction of psychological distress during times of stress, as well as it's effect on promoting psychological adjustment to a range of chronically stressful conditions. Being married or cohabiting with a significant other is a major source of social support and numerous studies have shown that married individuals have lower rates of morbidity and mortality compared with non-married individuals (Johnson et al., 2000; Kiecolt-Glaser & Newton, 2001). On the other hand, social isolation and loneliness have been related to high stress reactivity and inadequate physiological repair and maintenance processes (Hawkley & Cacioppo, 2003).

Studies in individuals with schizophrenia have demonstrated that they have smaller social networks overall as compared to healthy populations (Cohen & Sokolovsky, 1978; Hammer, 1981). Nonetheless, research has consistently documented the relationship between social support and outcome in individuals with schizophrenia [see (Buchanan, 1995) for a review]. For example, in a large Nordic sample of individuals with schizophrenia, Sorgaard and colleagues demonstrated that a larger social network was related to higher Global Assessment of Function (GAF) scores and fewer negative symptoms (Sorgaard et al., 2001). The correlational study design made it difficult to determine whether better overall functioning leads to more integrated social networks or whether larger social networks lead to better functioning. Longitudinal investigations provide some evidence that baseline social support predicts overall outcome. A study of 54 first-episode psychosis patients found that greater amounts of social support from nonkin individuals prior to treatment contact predicted adaptive functioning 1.5 and 5 years later (Erickson et al., 1998). This effect may, in part, be due to the possible buffering effects of social support on stress (Buchanan, 1995). Crits-

Cristoph (1987) found that individuals with schizophrenia who reported greater amounts of social support showed less vulnerability to the effects of everyday stress. Higher levels of social support have also been shown to be related to use of more adaptive coping strategies in individuals with schizophrenia (Macdonald et al., 1998b)

***Summary***

In summary, research has demonstrated that there are distinct psychological and physiological responses to stress, and that these processes appear to be linked. The interactions of these processes have not been explicitly investigated in schizophrenia, a disorder known to be significantly influenced by stress. Specifically, it is not known how the subjective experience of stress is related to appraisal and coping during a situation and how these processes influence the body's biological reaction to stress. In understanding the role of these factors in schizophrenia, it will be important not only to examine life stress and how these individuals cope with such stressors in daily life but also to investigate these processes under controlled situations.

This study systematically investigated the relationships among appraisal, coping strategies, cortisol secretion and perceived stress in a group of individuals with schizophrenia, individuals at genetic high-risk for schizophrenia and controls. Based on previous research, it is hypothesized that individuals with schizophrenia are more likely to appraise an event as a threat and use maladaptive coping strategies compared to controls. Consistent with the stress literature, the model predicts that individuals with schizophrenia are likely to show an abnormal cortisol response and perceive the event as more stressful than control participants, and that this is correlated with their appraisals and coping strategies. The model also predicts that use of coping strategies is related to

coping resources such as problem solving ability and social support, both of which have been previously reported to be diminished in individuals with schizophrenia. In other words, the model tested whether the abnormal HPA axis function in individuals with schizophrenia is related to their likelihood of making threat appraisals and using maladaptive coping strategies, when faced with a stressful event. It also tested whether their use of these coping strategies is in turn related to their reduced social network and diminished cognitive abilities. Since there has been little research on these factors in high-risk individuals, no specific hypotheses are proposed for this group.

## Chapter 3: Purpose, Research Design, Hypotheses

### *Purpose*

According to the stress-vulnerability model, the experience of stress is critical to the onset and/or maintenance of schizophrenia. It is nearly impossible to systematically study the causal impact of stress on the onset of schizophrenia; however, many correlational studies have investigated the relationship between stressful life events and psychosis, although results have been mixed. Some studies report an increased number of life events experienced prior to the onset of an acute psychotic episode (Bebbington et al., 1993; Brown & Birley, 1968; Canton & Fraccon, 1985; Chaven & Kulhara, 1988; Day et al., 1987; Mazure et al., 1997; Michaux et al., 1967; Scwartz & Myers, 1977) while others have not (Chung et al., 1986; Gruen & Baron, 1984). This body of literature has been criticized for its failure to account for daily variability of life stressors as well as its inability to explain differences between individuals in their reactions to stressful events.

A number of recent studies by Myin-Germeys and colleagues have investigated the impact of daily stressors and their relationship to psychotic symptoms in patients with schizophrenia, their first-degree relatives, and controls. Their unique design employed the experience sampling method to measure moment-to-moment variability in the experience of stress. No differences were found between patient relatives and community controls in the number of stressful events reported at various time points over six consecutive days. However individuals with schizophrenia reported experiencing more minor stressful events, especially those related to social situations. It is unclear whether individuals with schizophrenia encounter events that are qualitatively different than their asymptomatic relatives and controls or whether they are more likely to perceive benign or neutral events as stressful. According to Lazarus and Folkman (1984), stress is defined as "a particular relationship between a person and the environment that is appraised by the person as taxing or exceeding his or her resources or endangering his or her well-being." They argue that stress consists of three processes: (1) primary appraisal, which is the process of perceiving a threat to oneself, (2) secondary appraisal, which is the process of generating a response to the threat and (3) coping, which is the process of executing that response. Coping strategies may be influenced by any number of coping resources available to the person, including problem-solving skills or social support. Stress in any given situation can also be understood as the result of a cognitive appraisal process resulting in an emotional, physiological and behavioral stress response (Gaab et al., 2005). There is mounting evidence that individuals with schizophrenia experience more stress but it remains unclear whether such experiences are related to their appraisal of specific events, or use of ineffective coping strategies.

The purpose of this study was to systematically investigate differences in appraisal and coping strategies to daily life stressors in order to better understand differences in perceived stress among controls, individuals with schizophrenia, and individuals at genetic high-risk for developing schizophrenia. The study evaluated participants' appraisals and coping strategies to experimentally induced conditions of stress (i.e., engaging in role-plays and mental arithmetic tasks) as well as their usual coping strategies to everyday stressors. According to Lazarus and Folkman (1984), coping strategies may be related to coping resources, such as cognitive ability and social support. Previous research suggests that individuals with schizophrenia use different coping strategies than community controls (Horan et al., 2007; Ritsner et al., 2006) and that coping styles may be related to cognitive ability (Lysaker et al., 2004; Ventura et al., 2004). Other variables of interest include perceived stress, perceived social support, and physiological reactivity to stress. There is a great deal of evidence that individuals with schizophrenia have impairments in a range of cognitive functions (Heinrichs & Zakzanis, 1998). In addition, there is some evidence that social support lowers physiological reactivity (cortisol and heart rate) but not psychological reactivity to experimentally induced stress (Ditzen et al., 2007). This suggests a dissociation between physiological and psychological stress responses, although this relationship has not been exclusively studied. Exploratory analyses to elucidate the relationships among perceived stress, physiological reactivity to stress and social support will be conducted.

***Research Design***

Three groups of participants were recruited for the study: individuals with schizophrenia (SCZ), full biological siblings of individuals with schizophrenia (SIB) and

controls (CON). The SCZ group was comprised of individuals diagnosed with DSM-IV schizophrenia, who were stable (i.e., no acute changes in clinical status) and the CON group consisted of healthy individuals without a family history of psychotic disorders. All participants were between the ages of 18 and 50 and an effort was made to recruit a CON group demographically similar to SCZ.

All participants underwent one testing session lasting approximately 3.5 to 4 hours. First, participants engaged in a structured clinical interview (SCID) to determine diagnosis and study eligibility. For some participants, the interviewing clinician (ZD) made clinical ratings on the Scale of Positive Symptoms (SAPS) and Scale of Negative Symptoms (SANS). Eligible participants then filled out the following questionnaires: Life Events Questionnaire (LEQ), Hassles and Uplifts Scale (HSUP), Perceived Stress Scale (PSS), Interpersonal Support Evaluation List (ISEL) and Coping Responses Inventory (CRI). The first saliva sample was taken after participants filled out the above-mentioned questionnaires and were explained saliva collection procedures. Subsequent samples were collected approximately every 10 minutes thereafter for an hour. Participants were read standardized instructions for the Paced Auditory Sustained Attention Test (PASAT) and then asked to fill out the Primary Appraisal Secondary Appraisal Scale (PASA) and an abbreviated version of the Coping Responses Inventory (CRI). The PASAT was administered thereafter. Participants were asked the de-briefing questions (1. “On a scale of 1-10, how well do you think you did?” 2. “On a scale of 1-10, how stressful was this task?”) and then required to fill out the PANAS. After this, participants were explained the procedures for the role plays, including taping of the interaction. They were asked to fill out the PASA and abbreviated CRI . Then, they were

introduced to the confederate with whom they performed the role play. They were again asked the de-briefing questions (1. “On a scale of 1-10, how well do you think you did?” 2. “On a scale of 1-10, how stressful was this task?”) and then required to fill out the PANAS. Lastly, participants were administered the neuropsychological tests (WAIS-III – Vocabulary, Matrix Reasoning, Digit Span and Trail Making Test, Part B).

***Hypotheses***

Hypotheses related to group differences

1. SCZ and CON will not differ significantly in the number of major life events or weekly hassles but SCZ will report significantly more subjective stress associated with those events.

2. SCZ will perform significantly lower than CON on all neuropsychological variables: Vocabulary, Matrix Reasoning, Digit Span, and Trails B.

3. SCZ and CON will differ significantly in their physiological reactions to the PASAT and the role plays.

4. SCZ will be significantly more likely than CON to appraise the PASAT and the role plays as threats.

5. SCZ will be significantly more likely than CON to use avoidant coping strategies, when encountering general life stress as well as during the PASAT and the role plays.

6. SCZ will report significantly less social support than CON.

Hypotheses related to correlations

7. Coping styles will be related to affect associated with the PASAT and the role plays in both groups. Specifically, avoidance-coping will be related to negative affect.

8. Coping styles will be related to coping resources (cognitive ability and social support) in both groups. Specifically, approach-related coping will be associated with better cognitive ability and more social support.

9. Primary appraisals will be related to cortisol reactivity during the PASAT and the role plays in both groups.

Hypotheses related to mediation

10. Group differences in subjective stress / perceived stress will be mediated by general coping strategies, perceived social support and cognitive ability. Specifically, it is predicted that increased subjective stress will be associated with less approach coping, lower perceived social support and cognitive ability.

11. Group differences in perceived stress related to PASAT and role plays will be mediated by the following variables: cortisol reactivity, primary appraisal, and coping strategies, such that higher cortisol reactivity, threat appraisal, and avoidance coping will be associated with more perceived stress.

12. Group differences in coping styles will be mediated by coping resources (cognitive ability and social support). That is, more social support and better cognitive ability will be associated with more use of approach coping.

Secondary hypotheses regarding high risk groups

All hypotheses specified above were also tested in the SIB group. Individuals at genetic high-risk for developing schizophrenia tend to show similar patterns as SCZ on many variables. Therefore, it is hypothesized that SIB will be similar to SCZ on variables related stress, appraisal, coping, cortisol, and coping resources.

# Chapter 4: Method

## *Participants*

Human Subjects Involvement and Characteristics

Participants were 40 individuals who met DSM-IV criteria for schizophrenia and 40 community volunteers as healthy controls, matched to the individuals with schizophrenia on age, gender, race, and parental socioeconomic status. In order to explore the secondary hypotheses, 18 full siblings of individuals with schizophrenia were also recruited. Participants with schizophrenia were not in an acute phase (i.e., they were clinically stable). Participants with schizophrenia did not currently meet criteria for Major Depressive Disorder as depression is known to affect cortisol levels. Siblings of individuals with schizophrenia did not currently meet criteria for any DSM-IV psychotic disorders. Siblings and controls did not currently meet criteria for Major Depressive Disorder.

The inclusion criteria were: 1) age 18-50 years; 2) ability to give informed consent; and 3) meeting DSM-IV criteria for schizophrenia (SCZ); having no current or past personal or family history of psychiatric disorder (CON); not meeting DSM-IV diagnostic criteria for a psychotic disorder (SIB). The exclusion criteria were: 1) meeting DSM-IV criteria for current Major Depressive Disorder; 2) meeting DSM-IV criteria for substance abuse or dependence at any time within the past six months of enrollment; 3) presence of any clinically unstable or severe medical disorder that would make participation in the research protocol unsafe; 4) meeting DSM-IV criteria for mental retardation. For the two main groups of interest (SCZ and CON), participants were balanced for gender (i.e., 20 males, 20 females).

Recruitment and Informed Consent

SCZ and SIB were recruited from ongoing studies on schizophrenia at the Conte Center for the Neuroscience of Mental Disorders (CCNMD). The CCNMD has a large database of individuals with schizophrenia and their siblings who have participated in previous research studies led by Drs. Barch and Csernansky; these individuals had agreed to be contacted again for future research studies and were originally recruited from a range of outpatient facilities in the St. Louis area. In addition, the CCNMD has a database of individuals with schizophrenia who consented to be in research studies but did not meet inclusion criteria for specific research protocols. Some of these individuals were contacted and offered participation.

As with SCZ and SIB, CON were recruited from among those individuals participating in CCNMD projects. CON were also recruited through the Volunteers for Health database maintained by Washington University.

Informed consent was always obtained before an individual participated in any component of the protocol. All participants were given ample time to read the consent document, which was also explained verbally by trained research staff. Research staff members were available to answer questions about the study. The consent document contained a detailed description of all study procedures, as well as any possible risks and/or benefits. Participants were given the option to withdraw from the research study at will, even after consenting.

Diagnosis and Clinical Assessment

To determine each participant's diagnosis, a trained interviewer conducted a structured clinical interview with the Structured Clinical Interview for DSM-IV (SCID-

IV) (First et al., 2001). The SCID is considered the "gold standard" (Fenning et al., 1994) in diagnostic assessment and has modest to good inter-rater reliability (kappa ranges from .57 to 1.0) (Zanarini et al., 2000). The SCID-IV interviewer had access to any data from present and past hospital records and corroborative personal sources (e.g., family) contained in the individual's CCNMD file. All available data were combined to arrive at the diagnosis. In the case that a definitive diagnosis could not be reached by the interviewer, Dr. Barch was consulted for clinical guidance. All participants (SCZ, SIB, and CON) underwent an identical diagnostic process.

Medications

Ethical guidelines and laws in Missouri preclude withdrawing patients from medications. Therefore no changes were made to the participants' current treatment plans for this research study. Previous research has documented that antipsychotic medications depress cortisol levels (Cohrs et al., 2004; Meier et al., 2005; Popovic et al., 2007). However, to understand the effects of day to day stress and stress related coping in this population, it was important to assess participants on medications if this was their typical state. In other words, if individuals with schizophrenia are intended to be on medications, it would be more ecologically valid to assess how they appraise and cope with stressors in their daily life while on these medications. Nonetheless, to examine the potential influence of medication on stress appraisal and cortisol response, information on the type and dose of antipsychotic medications was obtained by the individual's verbal report. This allowed for secondary analyses comparing the effect of different classes of medications on the biological stress response.

## Measures

Variables of interest were measured with the following instruments:

### Stressful Events

Major life events were assessed with the Life Experiences Questionnaire (LEQ) (Norbeck, 1984; Sarason et al., 1978). This scale is known to have moderate test-retest reliability (r = .64) and adequate discriminant validity (Sarason et al., 1978). The LEQ is an 82-item questionnaire in which study participants marked the life events or changes that have occurred within the past year and indicated whether the events were considered *good* or *bad*. For the current study, the LEQ was modified to ask participants how stressful they experienced the event to be instead of asking how much impact the event had on their lives. Stress ratings were made on a 5-point likert scale in which 0 = *not stressful* and 4 = *extremely stressful*. Life events were grouped under the following categories: health, work, school, residence, love/relationships, family and close friends, parenting, personal/social, financial, crime and legal matters. Participants were also provided with space to note any events not listed on the questionnaire and indicate its effect and stress level.

Day-to-day stressors were assessed with the Hassles and Uplifts Scale (HSUP) (DeLongis et al., 1988). This scale consists of 53 items related to a broad range of everyday events (e.g., time spent with family, yard work, news events etc.) across eight areas: household, finances, work, home maintenance, health, personal life, family and friends, and environmental and social issues. Internal consistency, as measured by coefficient alpha, ranges from .80 to .93 across these eight factors. For this study, the HSUP was modified in the following ways: instead of rating the hassles or uplifts,

participants were asked if the item was experienced as *good* or *bad* and how stressful it was on a scale of 0 – 4 where 0 = *not stressful* and 4 = *extremely stressful*. This format is parallel to the LEQ and allowed for a more direct comparison between major and minor life events and associated stress. Participants rated items experienced within the past week.

Perceived stress was assessed with the Perceived Stress Scale (PSS) (Cohen et al., 1983), a 10-item questionnaire in which participants were asked to rate how often they felt a certain way in the past week (e.g., how often have you been upset because of something that happened unexpectedly? how often have felt that you could not cope with all the things you had to do? etc.). Cronbach's alpha coefficients for this scale range from 0.84 to 0.86 (Cohen et al., 1983). The PSS was modified to ask participants to make ratings based on the past week (instead of the past month) for more direct comparison with the HSUP.

Experimental Stressors

Participants underwent two procedures intended to invoke a brief stress response. These stressors involved mental arithmetic and social role plays and were chosen based on research suggesting they are most likely to produce a stress response. In a meta-analysis of 208 laboratory studies of psychological stressors, Dickerson and Kemeny (2004) found that acute stressors capable of eliciting cortisol responses had certain characteristics in common. They concluded that performance tasks were most likely to result in adrenocorticotropin hormone changes if they were uncontrollable and characterized by social-evaluative threat (i.e., task performance that could be negatively judged by others). Of the performance tasks, a combination of public speaking and

cognitive tasks resulted in the largest average effect size – twice as large as the effect size for cognitive tasks alone or tasks combining public speaking and verbal interactions. These tasks performed in the context of social-evaluative threat, in which the performance was videotaped, an evaluative audience was present or a person offering negative social comparison was present, resulted in significantly greater cortisol responses than those without these characteristics. The authors also tested whether there was a significant difference in effect size between studies with only one or more than one form of social evaluation. They reported that studies with only one form of social evaluation had an average effect size of 0.23, whereas those with two forms had an average effect size of 0.86. In terms of uncontrollability (characterized by task difficulty, false feedback, harassment or inescapable stimuli), there was no significant difference in cortisol response between those tasks that only had one element of uncontrollability versus those with several such elements. As noted above, tasks tapping elements of uncontrollability and social-evaluative threat had the largest effect size (0.92) and were found to be independent of each other in a simultaneous regression calculation.

For the current protocol, two different tasks were administered to achieve the characteristics of uncontrollability and social evaluation described above. Cortisol was measured in saliva at regular intervals before, during, and after the administration of these tasks (procedure described in detail below). A mental arithmetic test primarily served as an uncontrollable stressor. Participants were administered the Paced Auditory Serial Attention Test (PASAT) (Gronwall & Wrighston, 1974), a standardized test of attention that requires serial addition of digits presented verbally. Specifically, participants were required to add two sequentially presented single-digit numbers and say

the answer out loud. They had to retain the latter of the two numbers in memory for subsequent addition to the next number. Numbers ranging from 1 to 9 were delivered using a compact disc player to control the rate of stimulus presentation. Digits were presented every 2 seconds; 60 digits are presented in total. The PASAT places high demands on auditory working memory and is therefore perceived to be a difficult task. The perceived difficulty of this task, along with its standardized presentation on a CD player, lends some characteristics of uncontrollability to the PASAT. Previous studies that have used the PASAT for this purpose report that it induces "mild mental stress" (Phillips et al., 2006a; Ring et al., 2002). There is also an implicit social-evaluative threat associated with the fact that an administrator is present during the procedure and is recording the participants' responses, although the social role-plays were used primarily for social evaluation. Even though actual test performance was not related to a goal of the study, participants' responses were recorded. After the completion of the task, participants were asked the following questions: (1) How well do you think you did? (2) How stressful was this experience? Participants responded to the questions on a 10-point likert scale.

The other stressor, primarily with elements of social evaluation, involved participation in a role-play task. Participants were administered the Social Skills Performance Assessment (SSPA) (Patterson et al., 2001). The SSPA is a social role-play task that required participation in two 3-minute role-plays of selected social problem situations. The scenes were acted out between the participant and a confederate and videotaped for subsequent scoring (not proposed for this study). The SSPA consisted of three parts: (1) Practice Scene: A 1-minute interaction in which the participant was

making plans to get together with a friend (always played by the confederate). This scene served to acclimate participants to the testing situation and task demands. (2) Scene 1: A 3-minute interaction in which the participant was a tenant meeting a new neighbor (always played by the confederate). The objective was to greet the new neighbor and find out more information about him/her. (3) Scene 2: A 3-minute interaction in which the participant was a tenant calling his/her landlord (always played by the confederate) regarding a leak that has gone unrepaired after a previous complaint. The objective was to have the landlord attend to the leak immediately. For each scene, a description of the scenario to be enacted was presented to the participant on an index card. He/she was asked what role he/she was playing to ensure the task was properly understood. If the participant did not give the correct answer, a corrective prompt was provided. Upon a correct answer, the examiner indicated the beginning of the interaction. Confederate responses were standardized according to the SSPA manual and primarily entailed minimal, open-ended replies. This put the onus on the participant to maintain the interaction for 3-minutes. If the participant did not respond, the confederate offered a standardized prompt after 10 seconds to continue the conversation. Confederate responses during the role-play were characterized by non-facilitating comments for the first 2.5 minutes of the interaction (an example for scene 2: “I have a lot of other tenants with problems that are ahead of yours”). In other words, the confederate countered suggestions given by the participant without flatly refusing them for most of the interaction in order to allow participants to generate more solutions until a resolution was reached. This interaction was designed to be perceived by participants as negative judgment by the confederate and thus added a social-evaluative component to the task.

The fact that the interactions were videotaped added another social-evaluative component. All role-plays ended on a positive note in which the confederate agreed to cooperate with the participant. After the completion of the task, participants were asked the following questions: (1) How well do you think you did? (2) How stressful was this experience? Participants responded to the questions on a 10-point likert scale. As a mood repair precaution, participants were offered a variety of candy at the end of the session, after the last cortisol sample was collected, as unanticipated compensation for their participation in the research procedures.

Cognitive Appraisal

Cognitive appraisal of the experimental stressors was measured with the Primary Appraisal Secondary Appraisal Scale (PASA) (Gaab et al., 2005). The PASA is a 16-item questionnaire intended to measure the primary stress appraisals of threat and challenge as well as secondary appraisals related to self concept of own abilities and control expectancy. The items for this scale were generated to fit the theoretical constructs proposed by Lazarus and Folkman (1984). The PASA contains 8 items each on primary (PA) and secondary (SA) appraisals, on which participants evaluated the extent to which the particular statement applies to themselves on a 6-point scale ranging from *strongly disagree* to *strongly agree*. All items were re-worded to directly relate to the anticipated stressor. The scale has moderate to good internal consistency for both subscales (PA, $\alpha \geq 0.80$; SA. $\alpha \geq 0.74$) (Gaab et al., 2005). The PA scale of the PASA has been shown to predict significant variance in cortisol response to a public speaking task in healthy individuals (Gaab et al., 2005). Participants in this study were asked to fill out the PASA in anticipation of the PASAT and the role plays. For each task, participants were given

instructions on the upcoming task and participated in a brief practice task and then asked to fill out the PASA in anticipation of the actual task (i.e., before actually engaging in the task). The PASA was scored according to instructions from the developers.

Coping

Coping responses to specific experimental stressors as well as general life stressors were measured with the Coping Responses Inventory (CRI) (Moos, 1993). The CRI is a 48-item questionnaire assessing two broad types of coping responses: Approach Coping and Avoidance Coping. These two categories are further subdivided to yield four dimensions each: Approach = (1) Logical Analysis, (2) Positive Reappraisal, (3) Seeking Guidance and Support, and (4) Problem Solving; Avoidance = (5) Cognitive Avoidance, (6) Acceptance or Resignation, (7) Seeking Alternative Rewards, and (8) Emotional Discharge. All items were rated on a 5-point likert scale from 0 = *not al all* to 4 = *fairly often*. For the eight dimensions, Cronbach's alpha ranged from 0.58 to 0.74. In the current study, in order to assess participants' general coping strategies, they were asked to fill out the 48-item CRI in response to daily life stressors. An abbreviated 10-item CRI was administered for the PASAT and role plays separately, in order to assess which coping strategies were used during those experimental stressors. The abbreviated CRI contained 5 items each from the Approach and Avoidance Coping scales. Within these 2 domains, items were selected from the following subscales: Approach = (1) Logical Analysis and (2) Positive Reappraisal; Avoidance = (3) Cognitive Avoidance and (4) Acceptance or Resignation. These subscales, and the specific items within them, were chosen because of their applicability to the experimental stressors of this protocol. Items within the Seeking Guidance and Support, Problem Solving, Seeking Alternative

Rewards, and Emotional Discharge subscales did not relate to engaging in mental arithmetic or role-play tasks, and were therefore omitted from the abbreviated version. For example, the following items: *take it out on other people when you feel angry or depressed* (Emotional Discharge), *get involved in new activities* (Seeking Alternative Rewards), *talk with your spouse or other relative about the problem* (Seeking Guidance and Support) clearly cannot be applied to the tasks of engaging in the PASAT or role plays and therefore are not included in the abbreviated CRI.

Coping Resources

Two types of coping resources identified by Lazarus and Folkman (1984) were of primary interest to this study: social support and cognitive ability.

Social support was measured with the Interpersonal Support Evaluation List (ISEL) (Cohen & Hoberman, 1983; S Cohen et al., 1985). The ISEL consists of a list of 40 statements about the perceived availability of potential social resources and is rated on a 4-point scale ranging from 0 = *definitely false* to 3 = *definitely true*. The ISEL is counterbalanced for desirability, with half of the statements worded positively about social relationships (e.g., *there are several different people with whom I enjoy spending time*) and half worded negatively (e.g., *I feel that there is no one with whom I can share my most private worries and fears*). The ISEL was designed to assess the perceived availability of four separate functions of social support and contains 10 items each in the following 4 subscales: Tangible, which measures the perceived availability of material aid; Appraisal, which measures the perceived availability of someone to talk to about one's problems; Self-esteem, which measures the perceived availability of a positive comparison of one's self to others; and Belonging, which measures the perceived

availability of people one can engage with in social settings. The internal consistency of the total ISEL ranges from 0.88 to 0.90 and the internal consistency of the four individual subscales ranges from 0.62 to 0.82 (Cohen et al., 1985). The validity of the ISEL is documented with its significant correlations with number of close friends (0.46) and number of close relatives (0.42) in the general population (Cohen et al., 1985).

Cognitive ability was measured through the administration of standardized neuropsychological tests. The following cognitive domains were assessed: attention/working memory, verbal ability, mental flexibility, and abstract reasoning. Verbal ability was measured using the Vocabulary subtest of the Wechsler Adult Intelligence Scale – Third Edition (WAIS –III) (Wechsler, 1997). Abstract reasoning was measured with the Matrix Reasoning subtest of the WAIS-III. Attention/working memory was measured with the Digit Span subtest of the WAIS-III and mental flexibility was measured with Trail Making Test – Part B test of the Halstead-Reitan battery (Reitan & Wolfson, 1985).

Biological Measures

Cortisol was collected during the administration of the two experimental stressors and used as a measure of the HPA axis' response to stress. Cortisol levels were measured in saliva by asking participants to chew on a piece of cotton at the beginning of the experimental stressors session (i.e., after the diagnostic interview and completion of trait-based questionnaires) and approximately every 10 minutes thereafter for an hour. The cotton swab was stored in a tube until the end of the protocol, at which point it was centrifuged to extract the saliva. These saliva samples were stored at -20˚C until they

were sent for assays. Samples were de-identified of personal information and marked only with the subject ID, date, and time of collection.

Other Variables of Interest

A mood rating was collected after each experimental stressor to assess whether cognitive appraisal and coping strategies are correlated with mood. The Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988) was used to assess participants' mood related to stressors and administered directly after participation in the PASAT and then the role plays. The PANAS contains 2 subscales: A positive affect (PA) scale made up of 10 positive adjectives (e.g., interested, excited, proud, alert, etc.), and a negative affect (NA) scale made up of 10 negative adjectives (e.g., distressed, upset, irritable, nervous, etc.), which are rated on a 5-point likert scale ranging from 1 = *very slightly/not at all* to 5 = *extremely*. In reliability studies, Watson et al. (1988) administered the PANAS with time-frames ranging from "right now" to "during the last year" to a large, predominantly student, sample. The reliability of the PA scale ranged from .86 to .90, the NA scale from .84 to .87 (Watson & Clark, 1994). Its psychometric properties were independently evaluated by Crawford and Henry (2004) in a non-student population and the PANAS was again found to have good reliability ($\alpha = 0.89$ for PA and $\alpha = 0.85$ for NA). The authors also reported insignificant effects of demographic variables such as age, gender, occupation, and education on the PANAS. In the current study, participants were instructed to rate the strength of the emotions they felt while they were engaged in the role plays or the PASAT.

***Procedure***

Data was collected in one session of approximately 3.5 to 4 hours. Upon an initial phone screen to determine interest and general eligibility, participants were scheduled for an in-person assessment and experimental procedures. Verbal and written consent was obtained upon arrival. First, participants engaged in a structured clinical interview (SCID) to determine diagnosis and study eligibility. This process took about 45 – 60 minutes for SCZ and between 10 – 20 minutes for SIB and CON. Participants then filled out the following questionnaires: LEQ, HSUP, PSS, ISEL and CRI (complete version). This process took about 30 – 45 minutes.

Participants were then briefly informed of the experimental tasks and saliva sampling measures. They were asked to provide the first saliva sample by chewing on a cotton swab. Saliva samples were collected approximately every 10 minutes thereafter for an hour. A timer was set to ring every 10 minutes to alert the participant and the experimenter of the time to provide a sample. Participants were read standardized instructions for the PASAT. The instructions were repeated until the participant understood the task and a practice test was then administered. This ensured that participants fully understood what the task entailed. They were then asked to fill out the PASA and the abbreviated CRI. The PASAT was administered thereafter. Participants were asked the de-briefing questions (1. “On a scale of 1-10, how well do you think you did?” 2. “On a scale of 1-10, how stressful was this task?”) and then required to fill out the PANAS. After this, participants were explained the procedures for the role plays, including taping of the interaction. After instructions were given, they were introduced to the confederate with whom they would be performing the role play (the confederate was a trained research assistant who did not interact with the participants in any other way)

and the practice scene was administered to ensure that participants fully understand their role. They were then asked to fill out the PASA and the abbreviated CRI. Thereafter, they engaged in two 3-minute role plays with the confederate, which were videotaped. After the administration of the role plays, participants were asked the debriefing questions (1. "On a scale of 1-10, how well do you think you did?" 2. "On a scale of 1-10, how stressful was this task?") and then asked to fill out the PANAS. The administration of the experimental stressors took about 30 minutes.

Lastly, participants were administered the neuropsychological tests (WAIS-III – Vocabulary, Matrix Reasoning, Digit Span and Trail Making Test, Part B). This procedure took about 30 - 40 minutes.

***Data Reduction***

Variables of interest were computed in the following ways:

Major Life Events

The variables of interest were total number of events experienced in the past year (total life events) and total stress rating related to these events (total life stress). To derive the total life events variable, all events endorsed on the LEQ (collapsing across good and bad events) were added. Similarly, all stress ratings across these endorsed events were added to compute the total life stress variable.

Minor Life Events

The variables of interest were total number of events experienced in the past week (total weekly events) and total stress related to these events (total weekly stress). To derive the total weekly events variable, all events endorsed on the HSUP (collapsing

across good and bad) were added. All stress ratings across these endorsed events were added to compute the total weekly stress variable.

Perceived Stress

The variable of interest was total stress rating on the PSS. Total score was derived by reverse scoring 4 positively worded items (e.g., 0=4, 1=3, 2=2, 3=1, 4=0) and then summing across all 10 items.

Perceived Stress During Experimental Tasks

The variables of interests were perceived stress related to each task and perceived mastery of the tasks. Each was assessed by self-report on a 10-point scale after completion of the PASAT and role plays.

Cortisol

For cortisol parameters, areas under the curve (AUC) were calculated with respect to increase ($AUC_i$) and with respect to ground ($AUC_g$) using the trapezoidal method as an indicator of the integrated cortisol response to the experimental tasks (Pruessner et al., 2003). Given previous research findings (Gaab et al., 2005), all primary analyses with cortisol were computed using $AUC_i$.

Cognitive Appraisal

The PASA is made up of two primary scales: Primary Appraisal (PA) and Secondary Appraisal (SA). PA is further composed of two subscales: threat and challenge. Threat and challenge scores were computed separately by summing across items that make up those scales (Threat = items 1, 5, 9, 13; Challenge = items 2, 6, 10, 14).

Coping

The main variables of interest within the CRI were the approach-related and avoidance-related coping scores. For the full version of the CRI, these scores were calculated by summing across participant's ratings across the 24 items that make up these scales. For the abbreviated CRI, approach-related and avoidance-related coping scores were derived by summing across the 5 items that make up these scales.

Social Support

The ISEL is made up of four 10-item subscales. For this study, a total score was derived by reverse scoring (i.e., 3=0; 2=1; 1=2; 0=3) the following negatively-stated items: 6, 10, 11, 13, 14, 15, 17, 24, 25, 27, 28, 29, 30, 34, 35, 36, 39, 40 and then summing across all 40 items.

Cognitive Ability

All subtests of the WAIS-III were scored according to standardized instructions. Scaled scores, which correct for age and gender, were derived from the WAIS-III manual. For the Trail Making Test – Part B, a scaled scored corrected for age and education was derived using the Halstead-Reitan Professional Manual (Heaton et al., 2006).

Affect

The PANAS consists of 2 scales. The positive affect (PAf) score was derived by summing across participant's ratings on the following items: 1, 3, 5, 9, 10, 12, 14, 16, 17, 19. The negative affect (NAf) score was derived by summing across participant's ratings on the following items: 2, 4, 6, 7, 8, 11, 13, 15, 18, 20.

# Chapter 5: Results

A total of 104 participants were enrolled in the study. 3 were disqualified due to inadequate saliva production, 3 were disqualified due to current depression, and 1 was disqualified due to examiner error in task administration. Data from the remaining 97 participants is presented below.

**Demographic information**

40 SCZ, 40 CON and 17 SIB were included in the final analyses. The SCZ and CON groups were balanced on gender (i.e., 20 participants in each group were female). In the SIB group, 10 of 17 participants were female; gender composition of the groups was not significantly different, $\chi^2(2, N = 97) = .44$, $p > .05$. The groups also did not differ significantly on race, $\chi^2(2, N = 97) = 0.52$, $p > .05$. SCZ and CON did not differ significantly on age but SIB were significantly younger than both SCZ and CON, $F(2, 94) = 16.70$, $p > .01$. CON had significantly more years of education than SCZ and SIB, $F(2, 94) = 13.33$, $p < .01$ but the groups did not differ significantly on years of parental education, $F(2, 91) = 1.11$, $p > .05$. See Table 1 for demographic information.

Table 1. Demographic information for study participants

| | **CON (N = 40)** | | **SCZ (N = 40)** | | **SIB (N = 17)** | |
|---|---|---|---|---|---|---|
| Characteristic | *M* | *SD* | *M* | *SD* | *M* | *SD* |
| Age (years)^ | 35.6 | 9.5 | 37.8 | 8.8 | 24.3 | 3.7 |
| Gender (% female) | 50.0 | --- | 50.0 | --- | 58.8 | --- |
| Race (%African American) | 65.2 | --- | 70.0 | --- | 64.7 | --- |
| Education (years)* | 15.1 | 1.9 | 12.6 | 2.5 | 13.3 | 2.2 |
| Parental education (years) | 13.9 | 2.5 | 13.2 | 3.1 | 12.8 | 2 |

^ SIB < CON = SCZ ($p < .01$)

*CON > SCZ = SIB ($p < .01$)

***Outlier analysis***

A standard boxplot analysis, which identifies participants falling more than 3 standard deviations from the mean, was carried out for each variable of interest. Only two such variables had outliers among SCZ and CON: LEQ total items (total life events) and time to completion for Trails B. Two outliers were identified for LEQ total items and two outliers were identified for Trails B. For analyses involving these variables, data were analyzed with and without the outliers. Among SIB, one outlier was identified for $AUC_i$.

***Hypotheses related to group differences***

The first set of analyses examined group differences in SCZ and CON expected based on the published literature. It was necessary to establish these group differences in order to carry out the mediation analyses proposed above. In order to protect against the increased probability of a Type I error resulting from multiple comparisons, the Hotelling's T-square, a multidimensional analog of the univariate t-statistic, was computed, which provided an omnibus effect for each group of dependent variables.

*1. SCZ and CON will not differ significantly in the number of total life events or total weekly events but SCZ will report significantly more subjective stress (total life stress, total weekly stress, and perceived stress) associated with those events.*

There was a significant omnibus effect for a group difference in total events and total stress, Hotelling's Trace = 0.35, $F(14,174) = 2.16$, $p < .05$. Further analysis to determine which variables were driving the group difference revealed that CON reported significantly more weekly events within the last week compared to SCZ, $F(2,94) = 4.10$, $p < .05$, but SCZ reported significantly higher perceived stress within the last week, $F(2,94) = 5.52$, $p < .01$. SIB did not differ significantly from either CON or SCZ on

either of these variables; their responses fell in between those of CON and SIB (i.e., weekly events: CON > SIB > SCZ; perceived stress: SCZ > SIB > CON). There were no significant group differences for total life events, total life stress, average stress rating for those events, total weekly stress or the average stress rating for weekly events. This analysis was repeated without the two outliers identified for total life events and results remained unchanged. See Figures 1 and 2.

Figure 1. Group differences in major life events and total stress ratings associated with those events

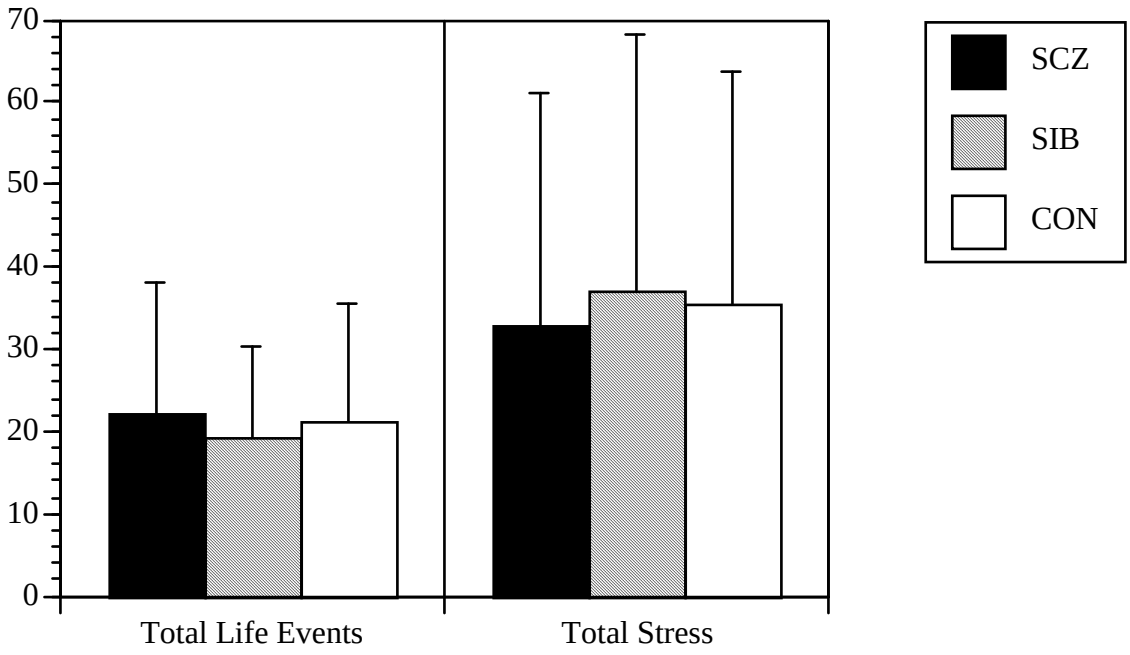
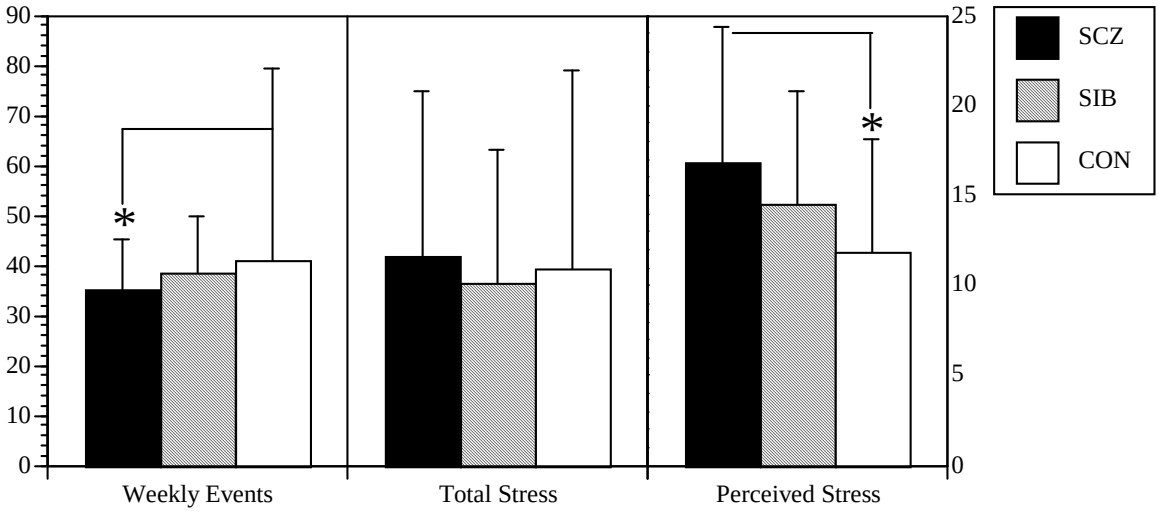


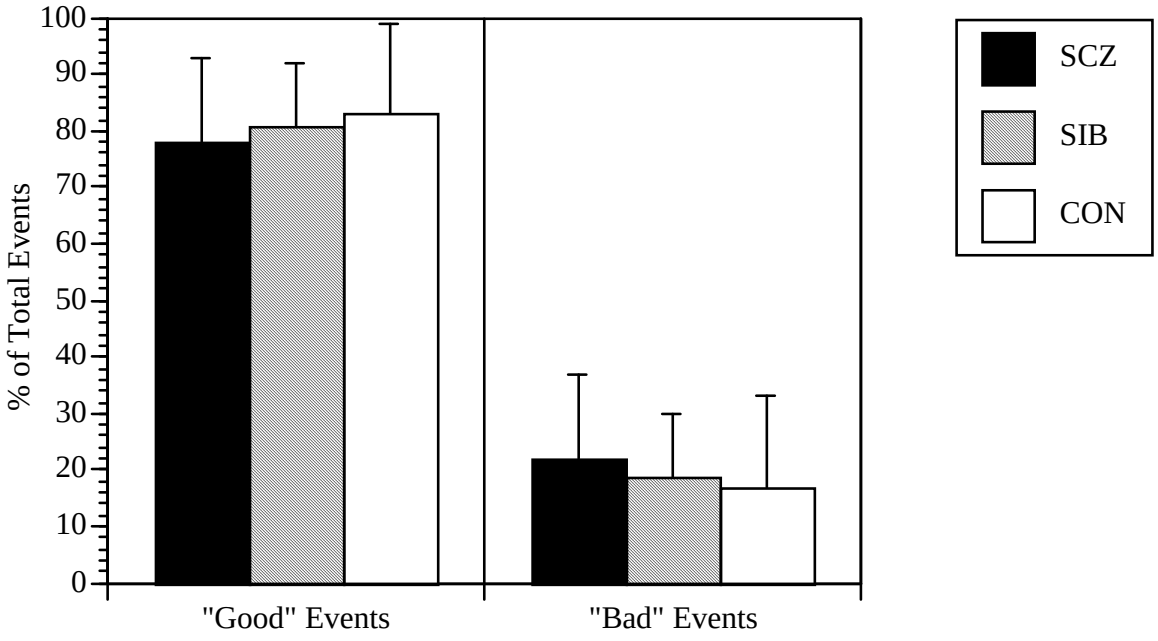
Figure 2. Group differences in weekly events, total stress ratings associated with those events and global perceived stress




A univariate analysis of variance (ANOVA) was computed to explore whether the groups differed in the number of total events endorsed as good and bad. There was no significant difference in the number of total life events endorsed as good, $F(2,94) = 0.59$, $p > .05$, or bad, $F(2,94) = 0.04$, $p > .05$, but there was a significant group difference in the number of weekly events endorsed as good, $F(2,94) = 4.76$, $p < .01$. Post hoc analyses revealed that CON were more likely than SCZ to report events in the past week as good ($p < .01$); SIB did not differ significantly from either group on this measure. There was no significant group difference in weekly events endorsed as bad, $F(2,94) = 0.17$, $p > .05$. Since CON reported significantly more weekly events overall than SCZ and significantly more good weekly events than SCZ, a proportional weekly events score was computed for each participant by dividing the number of weekly events endorsed as good or bad by the total number of events endorsed on the HSUP. There were no significant group

differences on these measures (*proportionally good*, $F(2,94) = 1.06$, $p > .05$; *proportionally bad*, $F(2,94) = 1.06$, $p > .05$.) See Figure 3.

Figure 3. Group differences in the proportion of weekly events rated as good or bad




In order to understand the relationships among objective and subjective stress variables on the weekly events questionnaire and subjective stress endorsed on the perceived stress scale, hierarchical regressions were computed to test whether these variables were correlated and whether the strength of these correlations differed by group. In order to carry out the regressions, two dummy coded variables were created (1 comparing CON to SCZ and SIB combined (D1) and the other comparing SIB to CON and SCZ combined (D2)). For each independent variable (IV) of interest, interaction terms were created by multiplying the IV with each dummy coded variable. Then, to test for correlation, the IV and the two dummy coded variables were entered in Step 1. The

two interaction terms were entered in Step 2. Thus, if the effect of the IV was significant in Step 1, it was interpreted as the two variables being significantly related. If either of the dummy coded variables were significant in Step 1, it was interpreted as there being a significant group difference in the DV. If group differences in a variable have already been reported, they are not repeated when stating results of the regression analyses. If either of the interaction terms were significant in Step 2, it was interpreted as the strength of the correlations being significantly different by group. In this case, the correlation was computed separately by group to examine how the magnitude of the correlation differed across groups.

There was no relationship between total items endorsed on the HSUP and perceived stress, $\beta = -.07$, $t$ (96) = -.71, $p > .05$, but there was a significant positive relationship between total stress reported on the HSUP and perceived stress, $\beta = .48$, $t$ (96) = 5.58, $p < .01$. There were no significant group differences in the strength of this relationship (all $p$s > .05). There was a significant negative relationship between number of proportionally good events and perceived stress, $\beta = -.52$, $t$ (96) = -5.49, $p < .01$, and a significant positive relationship between number of proportionally bad events and perceived stress, $\beta = .52$, $t$ (96) = 5.49, $p < .01$. There were no significant group differences in the strength of these relationships.

As mentioned above, for a subset of participants (64 of 97), data on current positive and negative symptoms was collected at the time of the assessment. As expected, SCZ displayed significantly more positive, $F(2, 61) = 29.77$, $p < .01$, and negative, $F(2, 61) = 22.40$, $p < .01$, symptoms than SIB and CON, and SIB displayed significantly more negative symptoms than CON ($p = .01$). Using the dummy code method, regression

analyses revealed that positive symptoms were significantly positively correlated with total stress reported on the HSUP, $\beta = .54$, $t\ (63) = 3.24$, $p < .01$, perceived stress in the past week, $\beta = .49$, $t\ (63) = 3.21$, $p < .01$, and events endorsed as proportionally bad, $\beta = .36$, $t\ (63) = 2.08$, $p < .05$. There were no group differences in the magnitude of the correlations. Positive symptoms were also significantly negatively correlated with events endorsed as proportionally good, $\beta = -.36$, $t\ (63) = -2.08$, $p < .05$, with no group differences in the magnitude of the correlations. Negative symptoms were not correlated with total stress endorsed on the HSUP, $\beta = .004$, $t\ (63) = .02$, $p > .05$ or with perceived stress in the past week, $\beta = .21$, $t\ (63) = 1.38$, $p > .05$, with no group differences in the magnitude of the correlations.

In summary, SCZ, SIB and CON did not differ in the number of events endorsed in the past year or on total stress associated with those events. CON reported more events in the past week than SCZ, especially events they endorsed as good, but there were no group differences in the proportion of events endorsed as good vs. bad or in total stress associated with those weekly events. Nonetheless, SCZ reported significantly more stress than CON in the past week on the perceived stress scale. Although the perceived stress scale was highly correlated with total stress reported on the HSUP and with proportion of weekly events endorsed as good or bad, it appears that the perceived stress scale captured constructs other than the amount of stress one can specifically associate with the occurrence of an event. High scores on positive symptom scales were also positively correlated with perceived stress; negative symptoms were not correlated with perceived stress.

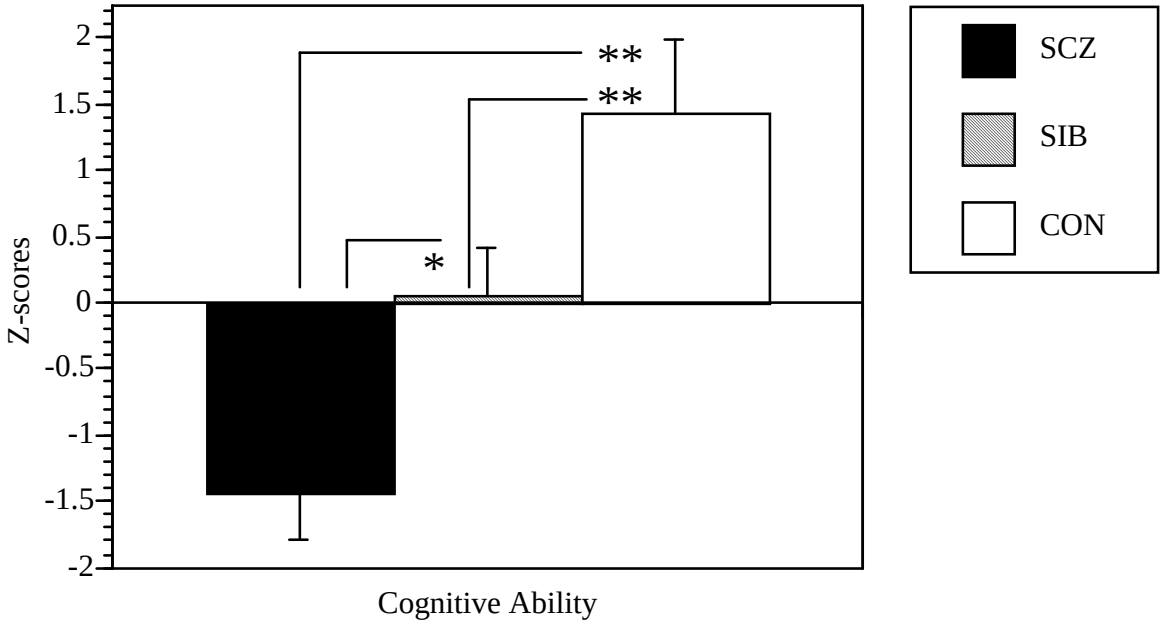
*2. SCZ will perform significantly lower than CON on all neuropsychological variables: Vocabulary, Matrix Reasoning, Digit Span, and Trails B.*

There was a significant omnibus effect for a group difference among the neuropsychological variables, Hotelling's Trace = 0.50, $F(8, 180) = 5.59$, $p < .01$. Further analysis of the data revealed that SCZ performed significantly better than CON on Vocabulary, $F(2, 94) = 8.99$, $p < .01$, Matrix Reasoning, $F(2, 94) = 8.16$, $p < .01$, Digit Span, $F(2, 94) = 10.03$, $p < .01$, and Trails B, $F(2, 94) = 13.46$, $p < .01$. In addition, SIB performed significantly worse than CON on Vocabulary ($p < .05$) and SIB performed significantly better than SCZ on Matrix Reasoning ($p < .05$) and Trails B ($p < .01$). The analysis was repeated with the outliers for Trails B omitted and results remained unchanged. In summary, the general pattern of performance was CON > SIB > SCZ, which replicated previous findings in the literature (Delawalla et al., 2006).

Bivariate correlations revealed that all four neuropsychological variables were significantly positively correlated with each other, $r(95) = .28$ to $r(95) = .61$, all $p$s $< .01$. Principal components analysis revealed only one factor with an eigenvalue greater than 1, incorporating about 60% of total variance. All four neuropsychological variables loaded highly on this factor. Thus, all four variables were z-scored and then averaged; this new variable was termed "cognitive ability" and used in the analyses reported below. An estimate of the reliability of this composite variable was computed using the formula described in Nunnally and Bernstein (1994) and found to be good ($r = .88$). As expected, an ANOVA showed that the groups differed significantly on this variable, $F(2, 94) = 15.77$, $p < .01$. CON performed significantly better than SIB and SCZ ($p < .01$) and SIB

performed significantly better than SCZ ($p < .05$); the pattern of performance was CON > SIB > SCZ. See Figure 4.

Figure 4. Group differences in composite variable "cognitive ability"

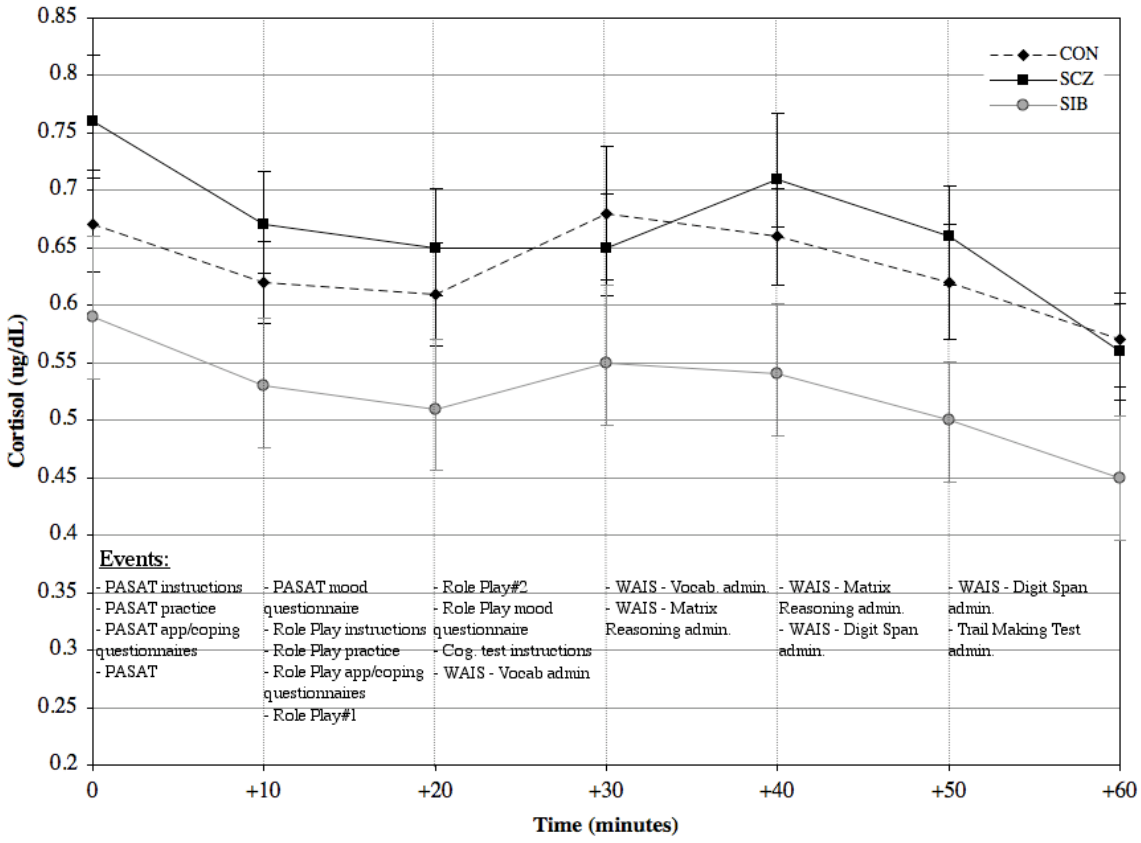



*3. SCZ and CON will differ significantly in their physiological reactions to the PASAT and the role plays.*

Of the 80 SCZ and CON participants from which adequate saliva was collected for cortisol assay, 5 were missing data at various timepoints, such that AUC measures could not be accurately computed from their data. An additional 4 participants were identified as outliers using standard box-plot analyses on at least one of the 7 saliva samples. 1 participant from the SIB group was also identified as an outlier. These individuals were excluded from all analyses concerning cortisol output or cortisol reactivity. Figure 5 shows cortisol data for SCZ and CON in relation to the order of events that occurred while saliva was sampled at 7 timepoints; 'time 0' refers to the baseline measure. In general, the effect of the stressor can be detected in salivary cortisol

about 10 – 15 minutes after its occurrence. Therefore, on the graph below, cortisol levels corresponding to the PASAT are represented between timepoints +20 and +30 and cortisol levels corresponding to role plays are represented between timepoints +30 and +40.

Figure 5. Cortisol collected before, during, and after stress induction procedure




Two formulas for obtaining an area under the curve were described above: $AUC_g$ (total cortisol output) and $AUC_i$ (cortisol increase over time). As expected, there was no correlation between the measures, $r(85) = .07$, $p > .05$, since they measure two different constructs. Thus, $AUC_g$ and $AUC_i$ were treated as separate variables and analyzed

separately. An ANOVA revealed no group difference in $AUC_g$, $F(2, 83) = 2.75$, $p > .05$, but planned contrasts showed that total cortisol output for SIB was significantly less than SCZ ($p < .05$). There were no significant group differences in $AUC_i$, $F(2, 83) = 1.67$, $p > .05$. Planned contrasts revealed that there was a trend for SCZ to have less increase in cortisol over time than CON ($p < .08$); pattern of cortisol increase over time was CON > SIB > SCZ.. Cohen's *d* was computed as a measure of effect size for $AUC_i$ comparing SCZ to CON and SIB to CON. The effect size was small to medium for both comparisons (SCZ vs. CON: $d = -.39$, SIB vs. CON: $d = -.36$).

Since these findings did not reach statistical significance, exploratory analyses were conducted to assess the contribution of individual differences factors known to possibly contribute to cortisol output such as: time of day of first sample, age, gender, and smoking habits. A dummy code regression method was used to examine the effects of each of these variables. In order to carry out the regressions, two dummy coded variables were created (1 comparing SCZ to CON and SIB combined [SCZvs.] and the other comparing SIB to CON and SCZ combined [SIBvs.]). For each independent variable (IV) of interest, interaction terms were created by multiplying the IV with each dummy coded variable. $AUC_i$ was entered as the DV. The IV and the two dummy coded variables were entered in Step 1. The two interaction terms were entered in Step 2.

As reported earlier, there was no significant group difference in the age of participants in SCZ and CON groups but SIB were significantly younger than SCZ and CON. In the regression, there was no effect of age on $AUC_i$, $\beta = .20$, $t(96) = 1.58$, $p > .05$. The group by age interaction terms were also not significant (SCZvs., $\beta = .09$, $t(96) = .18$, $p > .05$, SIBvs., $\beta = .23$, $t(96) = .35$, $p > .05$). An ANOVA revealed that the first

baseline sample for SIB was obtained later in the day (SCZ = 11:38 AM, CON = 11:37 AM, SIB = 12:57 PM), $F(2, 88) = 3.28$, $p < .05$. Planned pairwise comparisons confirmed that the effect was significant ($p < .05$) when comparing just SIB to CON and just SIB to SCZ. In the regression, there was no effect of time of baseline sample on $AUC_i$, $\beta = -,07$, $t\ (96) = -.64$, $p > .05$. The group by time interaction terms were also not significant (SCZvs., $\beta = .85$, $t\ (96) = 1.13$, $p > .05$, SIBvs., $\beta = -.36$, $t\ (96) = -.35$, $p > .05$). There was also no significant group difference in baseline cortisol, $F(2, 85) = 2.06$, $p > .05$. Collapsing across groups, there was no significant difference in $AUC_{i,}$ between males and females, $t\ (68) = 1.08$, $p > .05$. In the regression, there was no effect of gender on $AUC_i$, $\beta = -.13$, $t\ (96) = -1.19$, $p > .05$. The group by gender interaction terms were also not significant (SCZvs., $\beta = .41$, $t\ (96) = 1.09$, $p > .05$, SIBvs., $\beta = -.10$, $t\ (96) = -.25$, $p > .05$). There was a significant group difference in the average number of cigarettes smoked per day, $F(2, 88) = 6.29$, $p < .01$, with SCZ smoking significantly more than CON ($p < .01$) and SIB ($p < .05$). In the regression, there was no effect of cigarettes per day on $AUC_i$, $\beta = -.14$, $t\ (96) = -1.19$, $p > .05$. The group by cigarettes per day interaction terms were also not significant (SCZvs., $\beta = -.12$, $t\ (96) = -.37$, $p > .05$, SIBvs., $\beta = .06$, $t\ (96) = .54$, $p > .05$).

Among SCZ, medications are also known to affect cortisol secretion. During the assessment, verbal report of current medications and dosage information was documented. However, since there has not yet been a validated system for equating doses for atypical antipsychotics, data were analyzed by grouping antipsychotic medications into: 1) None (no antipsychotics), 2) Atypical Only (may include other psychotropics but not typical antipsychotics) and 3) Typical (may include atypical antipsychotics and/or

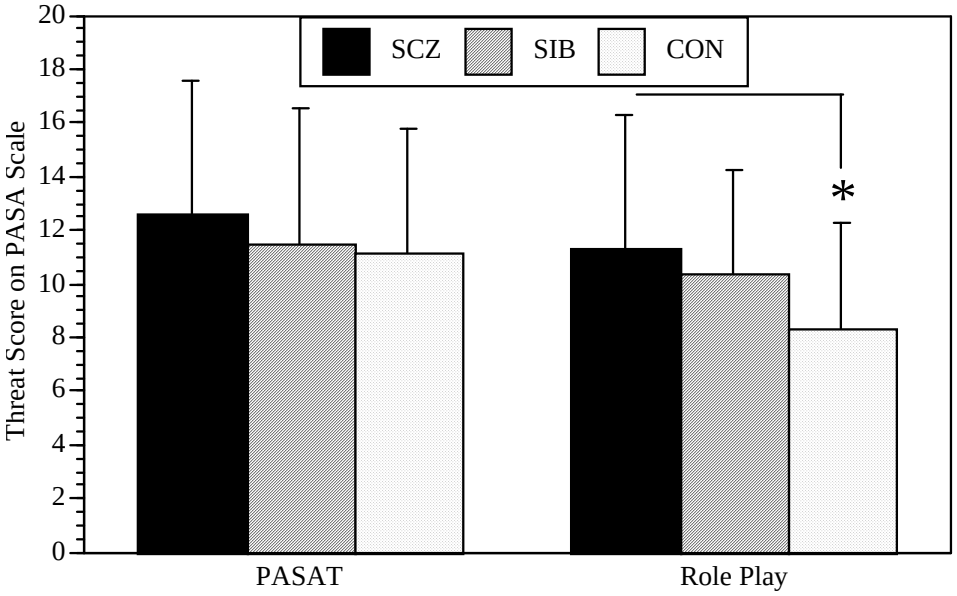
other psychotropics). Among the 36 SCZ participants who had adequate cortisol data, 2 were classified under None, 27 under Atypical only and 7 under Typical. An ANOVA revealed no group difference in $AUC_i$ as a function of type of antipsychotic medication, $F(2, 33) = 1.70$, $p > .05$. Effect of antidepressant medication on cortisol was investigated in a similar manner. Participants were classified as: 1) None (no antidepressant medications, may be on antipsychotics and other psychotropics), 2) Antidepressant only (no other psychotropics) and 3) Antidepressant + Antipsychotics (atleast one antidepressant and one antipsychotic). Of the 36 SCZ participants with cortisol data, none were on antidepressants only, 22 were not on any antidepressants, and 14 were on antidepressants and antipsychotics. An independent samples t-test revealed that among SCZ, those on antidepressants and antipsychotics had significantly lower $AUC_i$ than those on antipsychotics alone (no antidepressants), $t(34) = 1.92$, $p < .05$. However, when antidepressant status was entered as a covariate in an ANOVA, no significant group differences were observed in $AUC_i$, $F(2, 68) = .62$, $p > .05$. Among SCZ, there was no relationship between $AUC_i$ and positive symptoms, $r(19) = -.17$, $p > .05$, or negative symptoms, $r(19) = -.18$, $p > .05$.

In summary, as expected, SCZ showed less cortisol reactivity to experimental stressors than CON ($d = -.39$), but results did not reach statistical significance even after controlling for various individual differences factors. SIB were intermediate between SCZ and CON in terms of cortisol reactivity.

*4. SCZ will be significantly more likely than CON to appraise the PASAT and the role plays as "threats."*

There was a trend level group difference in PASAT and role play threat scores, Hotelling's Trace = 0.09, $F(4, 184) = 2.14$) $p < .08$. Planned contrasts revealed that SCZ were more likely than CON to appraise both the PASAT and the role plays as threats, but the difference only reached significance for role play appraisals, $F(1, 78) = 7.55$, $p < .01$. See Figure 6. There was a significant omnibus effect for challenge scores, Hotelling's Trace = .16, $F(4, 184) = 3.63$, $p < .01$. Planned contrasts revealed that SCZ were significantly more likely to make challenge appraisals on role play than CON ($p < .05$) and SIB ($p < .01$).

Figure 6. Threat appraisal scores on experimental stressors




To examine the relationship between threat and challenge appraisals, the dummy code regression method described under hypothesis 1 was used to investigate whether these variables were correlated and whether there was a significant group difference in the strength of this relationship. In order to simplify presentation, bivariate correlations

were first computed combining all groups to test whether threat appraisals on PASAT were related to threat appraisals on role plays and whether challenge appraisals on PASAT were related to challenge appraisals on role plays. Threat appraisals on one stressor were significantly positively correlated with stress appraisal on the other stressor, $r(95) = .32$, $p < .01$, and challenge appraisals on one stressor were significantly positively correlated with challenge appraisals on the other, $r(95) = .32$, $p < .01$. Given these results, the two threat variables and two challenge variables were combined into one threat variable and one challenge variable by z-scoring and then averaging the variables (threat $\alpha = .48$, challenge $\alpha = .48$). These composite variables were then entered into a regression, as described above. There was no relationship between threat appraisals and challenge appraisals, $\beta = .07$, $t(95) = .65$, $p > .05$.

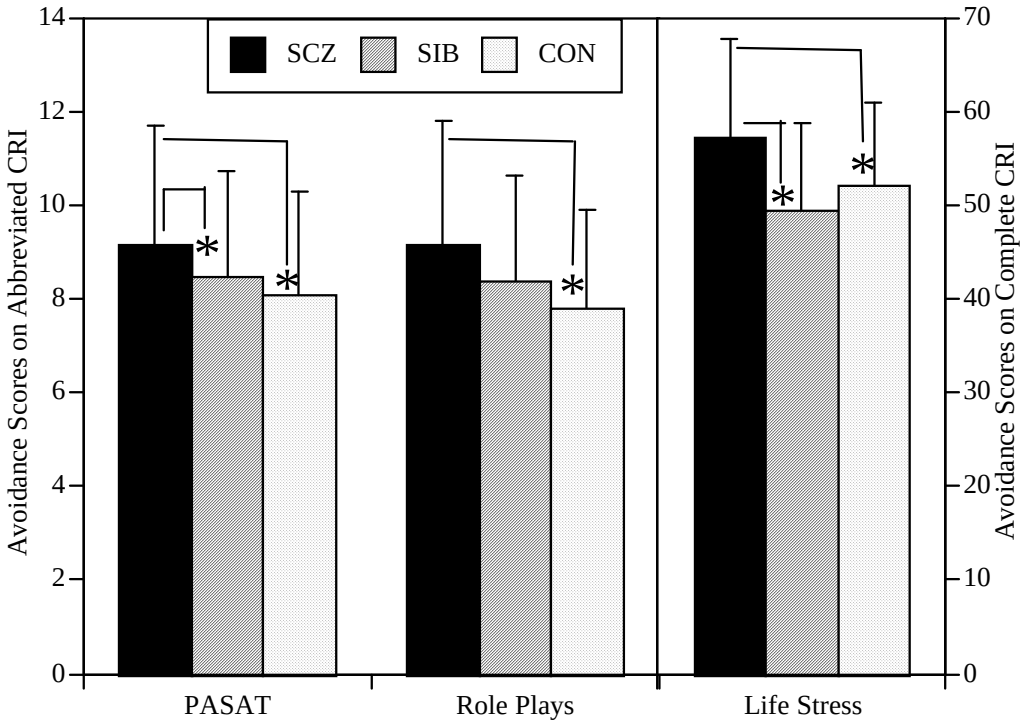
In summary, there was a trend for SCZ to appraise role plays, but not the PASAT, as more threatening than CON and SIB. SCZ were also significantly more likely to appraise role plays, but not PASAT, as more challenging than CON and SIB. There was no relationship between threat appraisals and challenge appraisals, although threat scores on one stressor were significantly positively correlated with threat scores on the other stressor and challenge scores on one stressor were significantly positively correlated with challenge scores on the other stressor.

*5. SCZ will be significantly more likely than CON to use avoidant coping strategies, when encountering general life stress as well as during the PASAT and the role plays.*

There was a significant omnibus effect for a group difference in coping strategies, Hotelling's Trace = 0.42, $F(12, 176) = 3.06$, $p < .01$. Planned pairwise comparisons revealed that SCZ were significantly more likely than CON to use avoidant coping

strategies when faced with general life stress ($p < .05$), as well as during PASAT ($p < .05$) and role plays, ($p < .05$). CON were significantly more likely than SCZ to use approach-related coping strategies when faced with general life stress ($p < .05$) but not during PASAT ($p > .05$) or role plays ($p > .05$). CON were significantly more likely than SIB to use approach coping to general life stress ($p < .01$), as well as during the PASAT ($p < .01$) and role plays ($p < .01$). On role plays, SIB were less likely than SCZ to use approach coping ($p < .01$). SIB were less likely than SCZ to use avoidance coping to general life stress ($p < .01$). See Figure 7.

Figure 7. Use of avoidance-related coping strategies while facing general life stress and during experimental stressors.




The dummy code regression method described above was used to investigate inter-relationships among avoidance- and approach-coping variables. Before computing these regressions, bivariate correlations combining all groups were computed to see

whether approach coping on one stressor was related to approach coping on the other and whether avoidance coping on one stressor was related to avoidance coping on the other stressor. PASAT approach was significantly positively correlated with role play approach, $r(95) = .59$, $p < .01$, and PASAT avoidance was significantly positively correlated with role play avoidance, $r(95) = .57$, $p < .01$. Thus the two approach and avoidance variables were combined into one approach and avoidance variable by z-scoring and then averaging the two related variables (approach $\alpha = .74$, avoidance $\alpha = .73$). These new composite variables were used to examine whether approach coping during the stressors was related to avoidance coping during the stressors and whether coping during experimental stressors was related to coping in response to general life stress. There was no relationship between approach coping during the stressors and avoidance coping during the stressors, $\beta = .18$, $t$ (95) = 1.83, $p > .05$, but there was a significant positive relationship between approach coping to general life stress and avoidance coping to general life stress, $\beta = .38$, $t$ (95) = 3.92, $p < .01$, and the strength of this relationship was different among CON, SIB and SCZ. Separate bivariate correlations for each group revealed that approach and avoidance coping were significantly correlated in SCZ, $r(38) = .54$, $p < .01$, but not in CON $r(38) = .22$, $p > .05$ or SIB $r(15) = .10$, $p > .05$. There was a trend for approach coping to life stress to be related to approach coping during experimental stressors, $\beta = .20$, $t$ (95) = 1.91, $p < .06$ with no significant group difference in the strength of the relationship. Avoidance coping to life stress was also related to avoidance coping during the stressors, $\beta = .29$, $t$ (95) = 3.04, $p < .01$, with no significant group differences in the strength of the relationship. Approach coping to life stress was not related to avoidance coping during experimental stressors, $\beta = .03$, $t$ (95) =

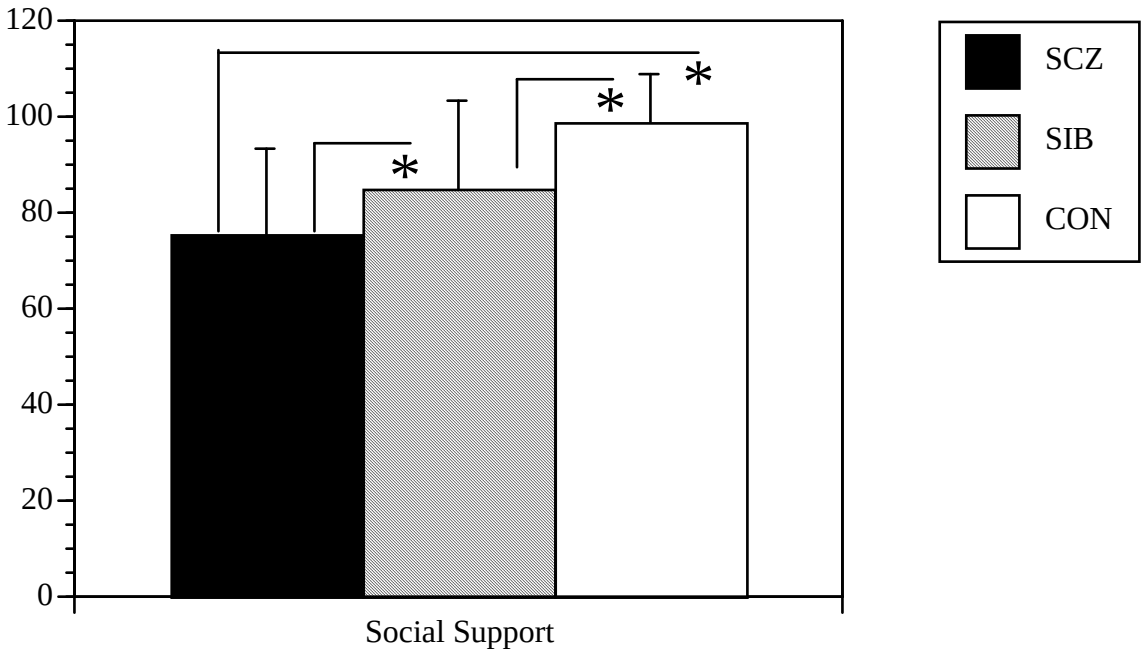
.27, $p > .05$, and avoidance coping to life stress was not related to approach coping during experimental stressors, $\beta = .19$, $t$ (95) = 1.92, $p > .05$.

In summary, as predicted, SCZ reported more avoidant-related coping than CON for general life stress and during the experimental stressors. In addition, SCZ reported less approach-related coping than CON for general life stress. SIB reported significantly less approach coping than CON for general stress and experimental stressors. SIB fell in between SCZ and CON in their use of avoidant coping on the experimental stressors. General approach-related coping was significantly positively related to general avoidance coping, but only among SCZ. General approach coping was not related to avoidance coping during experimental stressors. There was a significant positive correlation between use of approach or avoidant coping during experimental stressors and use of those strategies in response to general life stress. In other words, those who use avoidant coping strategies in general were also more likely to use avoidant coping strategies during experimental stressors.

*6. SCZ will report less social support than CON.*

An ANOVA revealed significant group differences in social support, $F(2, 94) = 22.66$, $p < .01$. Planned contrasts confirmed that SCZ reported significantly lower social support than CON ($p < .01$) and SIB ($p < .05$) and SIB reported significantly lower social support than CON ($p < .01$). See Figure 8.

Figure 8. Group differences in perceived social support




***Hypotheses related to correlations***

All correlations were computed using the dummy code regression method described above.

*7. Coping styles will be related to affect associated with the PASAT and the role plays in all groups. Specifically, avoidance-coping will be related to negative affect.*

For the PASAT, approach coping was significantly positively associated with positive affect, $\beta = .51$, $t(95) = 6.00$, $p < .01$, with no significant group differences in the strength of the relationship. Approach coping was not related to negative affect, $\beta = -.08$, $t(95) = -.81$, $p > .05$. Avoidance coping was negatively associated with positive affect, $\beta = -.20$, $t(95) = -2.05$, $p < .05$, and the magnitude of the relationship was significantly different among the groups ($p < .01$). Separate bivariate correlations revealed that avoidance coping was significantly inversely related to positive affect in all three groups:

SCZ = $r(38) = -.33$, $p < .05$, CON = $r(38) = -.28$, $p < .05$, SIB = $r(15) = -.46$, $p < .05$, but the strength of this association was greatest in the SIB. Avoidance coping was positively correlated with negative affect, $\beta = .27$, $t(95) = 2.70$, $p < .01$, with no group differences in the strength of the relationship.

For role plays, approach coping was significantly positively correlated with positive affect, $\beta = .25$, $t(95) = 2.64$, $p = .01$, with no significant group differences in the strength of the relationship. Approach coping was not related to negative affect, $\beta = .15$, $t(95) = 1.48$, $p > .05$. Avoidance coping was not related to positive affect, $\beta = -.12$, $t(95) = -1.30$, $p > .05$, but significantly positively related to negative affect, $\beta = .42$, $t(95) = 4.64$, $p < .01$. There was no group difference in the strength of this relationship.

In summary, approach coping was related to positive affect and avoidance coping was related to negative affect during both experimental stressors. See Table 2 for standardized beta weights for the relationships among coping and affect variables.

Table 2. Correlations between affect and coping strategies used during experimental stressors.

| | | Approach Coping | Avoidance Coping |
|---|---|---|---|
| PASAT | Positive Affect | .51** | -.20* |
| | Negative Affect | -.08 | .27** |
| Role Plays | Positive Affect | .25** | -.12 |
| | Negative Affect | .15 | .42** |

*8. Coping styles will be related to coping resources (cognitive ability and social support) in both groups, Specifically, approach-related coping will be associated with better cognitive ability and more social support.*

There was no relationship between approach coping and cognitive ability $\beta = .04$, $t(95) = .42$, $p > .05$, but approach coping was significantly positively related to social support, $\beta = .32$, $t(95) = 3.82$, $p < .01$. The strength of this relationship was different in CON vs. SIB and SCZ ($p < .05$). Separate bivariate correlations revealed that approach coping and social support were significantly related in SCZ, $r(38) = .49$, $p < .01$, but not in CON, $r(38) = .16$, $p > .05$, or SIB, $r(15) = .23$, $p > .05$. Avoidance coping was not related to cognitive ability, $\beta = -.08$, $t(95) = -.83$, $p > .05$ or social support, $\beta = .05$, $t(95) = .53$, $p > .05$. See Table 3.

Table 3. Correlations among cognitive ability, social support and coping variables

| | Approach Coping | Avoidance Coping |
|---|---|---|
| Cognitive Ability | .04 | -.08 |
| Social Support | .32** | .05 |

** correlation only sig. in SCZ ($p < .01$)

*9. Primary appraisals will be related to cortisol reactivity during the PASAT and the role plays in both groups.*

Correlations were computed for $AUC_i$ and the composite threat and challenge scores derived from threat and challenge scored during PASAT and role plays. Cortisol reactivity was not related to threat appraisals, $\beta = -.01$, $t(85) = -.08$, $p > .05$, but positively

related to challenge appraisals, β = .26, $t(85) = -2.50$, $p < .05$. The strength of this relationship differed significantly among SIB vs. CON and SCZ ($p < .01$). Bivariate correlations revealed that this relationship was significant among CON, $r(38) = .33$, $p < .05$ but not SCZ, $r(38) = .19$, $p > .05$ or SIB, $r(15) = -.15$, $p > .05$. See Table 4.

Table 4. Correlation among cognitive appraisal variables and cortisol reactivity

| | Cortisol Reactivity |
|---|---|
| Threat Appraisal | -.01 |
| Challenge Appraisal | .26* |

* correlation only sig. in CON ($p < .05$)

***Hypotheses related to mediation***

*10. Group differences in subjective stress / perceived stress will be mediated by general coping strategies, perceived social support and cognitive ability. Specifically, it is predicted that increased subjective stress will be associated with less approach coping, lower perceived social support and cognitive ability.*

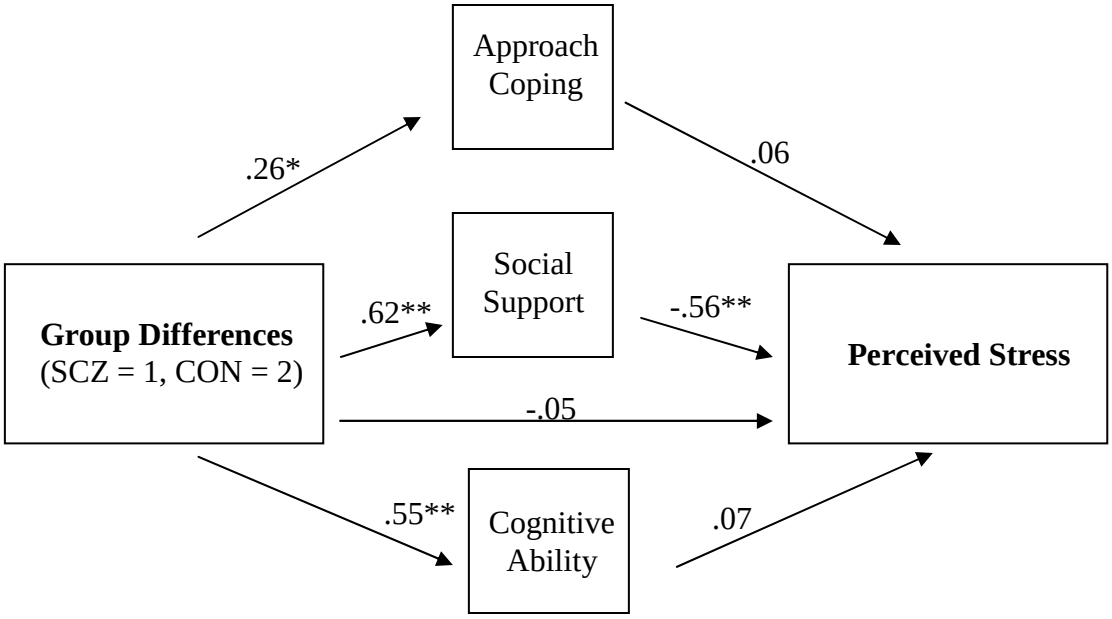
Of all the subjective stress variables, only stress reported on the perceived stress scale was significantly different between CON and SCZ. Therefore, only this variable was used as the outcome variable. Since SIB did not differ significantly from CON or SCZ on perceived stress, they were not included in the mediation analysis. As reported above, the three potential mediator variables all showed the expected group differences: 1) CON were significantly were more likely to use approach-related coping to general life stress as compared to SCZ; 2) CON also reported significantly greater perceived

social support; and 3) CON had greater cognitive ability than SCZ. Bivariate correlations were computed to test whether the mediator variables (approach-coping, social support and cognitive skills) were related to the outcome variable (perceived stress). Perceived stress was significantly negatively related to approach-coping, $r(78) = -.21$ $p < .05$, social support, $r(78) = -.53$, $p < .01$, and cognitive ability, $r(78) = -.21$ $p < .05$).

These variables were then entered into a series of regression equations to test for mediation. As stated above, group was entered as the independent variable, perceived stress was entered as the dependent variable, and approach-coping, social support, and cognitive ability were entered as mediators. Following the guidelines of McKinnon (2008), the first regression equation was used to regress the effect of perceived stress (DV) on group (IV), $\beta = -.35$, $t(78) = -3.28$, $p < .01$. Next, perceived stress (DV) was regressed on group (IV), $\beta = -.05$, $t(75) = -.40$, $p > .05$, as well as all of the mediators: approach-coping, $\beta = .05$, $t(75) = .50$ $p > .05$, social support, $\beta = -.56$, $t(75) = -4.04$, $p < .01$, and cognitive ability, $\beta = .07$, $t(75) = .61$, $p > .05$. In the next set of equations, each mediator was independently regressed on perceived stress (approach coping: $\beta = .26$, $t(78) = 2.34$, $p < .05$; social support: $\beta = .62$, $t(78) = 7.03$, $p < .01$; cognitive: $\beta = .55$, $t(78) = 5.81$, $p < .01$). Using the formulas described in MacKinnon (2008), the global and specific mediated effects were computed for these variables. In this model, there was a significant global mediated effect equal to -4.246 (95% CI = -1.84 to - 6.66). The specific mediated effect was significant for social support (5.021, 95% CI = -7.82 to -2.22), but not for approach-coping (.203, 95% CI = -.62 to 1.02), or cognitive ability (.569, 95% CI = -1.28 to 2.42). Further, given that group no longer significantly predicted perceived stress once the mediators were in the model, $\beta = -.05$, $t(76) = -.40$, $p > .05$,

there was full mediation of the effect of group (SCZ vs. CON) on perceived stress and this effect appeared to be primarily driven by social support. See Figure 9.

Figure 9. Multiple mediator model of group differences in perceived stress




*11. Group differences in perceived stress related to PASAT and role plays will be mediated by the following variables: cortisol reactivity, primary appraisal, coping strategies, such that higher cortisol reactivity, threat appraisal, and avoidance coping will be associated with more perceived stress.*

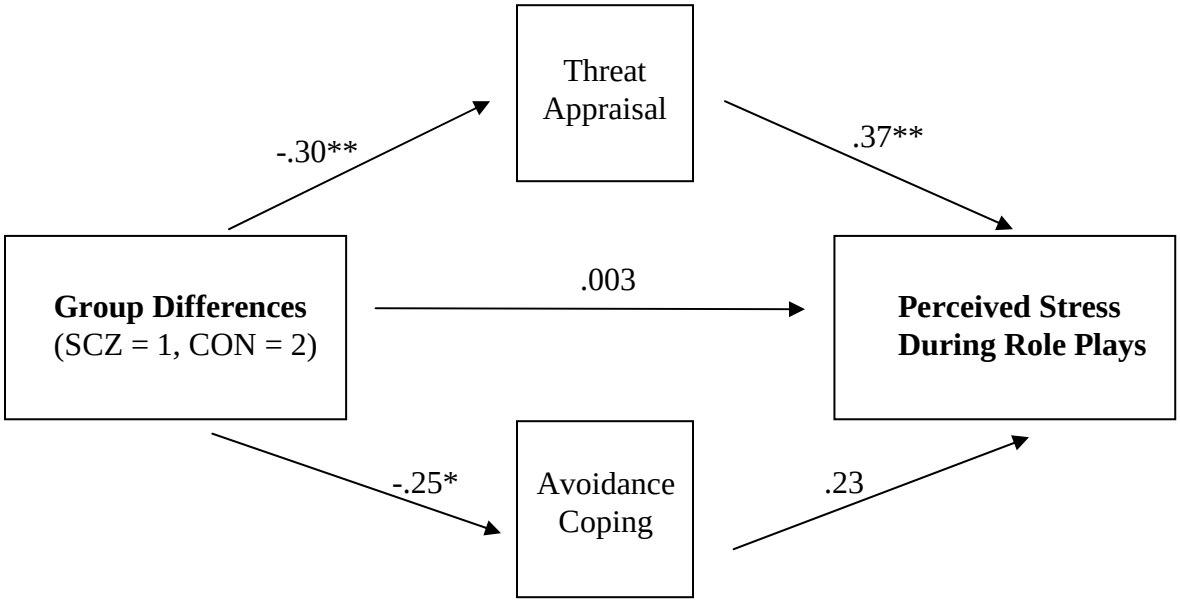
For both experimental stressors, SCZ reported feeling more stressed than CON and SIB, but the difference was not significant for either the PASAT, $F(2, 94) = .83$, $p > .05$, or the role plays, $t(2, 94) = 1.44$, $p > .05$. Since the primary hypotheses were about SCZ and CON, independent t-tests were carried out to explore differences in perceived stress among just these groups. Again, the groups did not differ on reported stress during

PASAT, $t(78) = .43$, $p > .05$, but there was a trend for SCZ to report higher stress during role plays $t(78) = 1.45$, $p < .08$. Thus, mediation was tested for perceived stress during role plays for CON and SCZ. As reported above, SCZ were significantly more likely to appraise role plays as threats, and use more avoidance coping strategies than CON but showed less cortisol reactivity than CON. Bivariate correlations were computed to test whether the mediator variables ($AUC_i$, role play threat appraisal and role play avoidance coping) were related to the outcome variable (role play subjective stress). Subjective stress on the role plays was significantly positively related to threat appraisal, $r(78) = .46$, $p < .01$, and avoidance coping, $r(78) = .38$, $p < .01$, but not related to cortisol reactivity, $r(73) = .01$, $p > .05$. As such, cortisol reactivity was not included in the mediation model.

The other two mediator variables were then entered into a series of regression equations to test for mediation. Group was entered as the independent variable, subjective stress during role play was entered as the dependent variable, and threat appraisal of role play and avoidance coping during role play were entered as mediators. The first regression equation was used to regress the effect of subjective stress during role play (DV) on group (IV), $\beta = -.16$, $t(78) = -1.45$, $p < .2$. Next, subjective stress during role play (DV) was regressed on group (IV), $\beta = .003$, $t(78) = .03$, $p > .2$. as well as the two mediators: threat appraisal, $\beta = .37$, $t(78) = 3.27$, $p < .01$, and avoidance coping, $\beta = .23$, $t(78) = 2.05$, $p < .05$. In the next set of equations, each mediator was independently regressed on subjective stress during role play (threat appraisal: $\beta = -.30$, $t(78) = -2.78$, $p < .01$; avoidance coping: $\beta = -.25$, $t(78) = -2.27$, $p < .05$). Again, using the formulas described in MacKinnon (2008), the global and specific mediated effects were computed for these variables. In this model, there was a significant global mediated effect of -.916

(95% CI = -1.61 to - .22). The specific mediated effect was significant for threat appraisal = -.60 (95% CI = -1.16 to -.04), but not for avoidance coping = -.31 (95% CI = -.71 to .09). The effect of group on subject stress was no longer significant, with the mediators in the model, $\beta = .003$, $t(78) = .03$, $p > .05$). suggesting full mediation that was primarily driven by threat appraisal. See Figure 10.

Figure 10. Multiple mediatior model for group differences in perceived stress during role plays



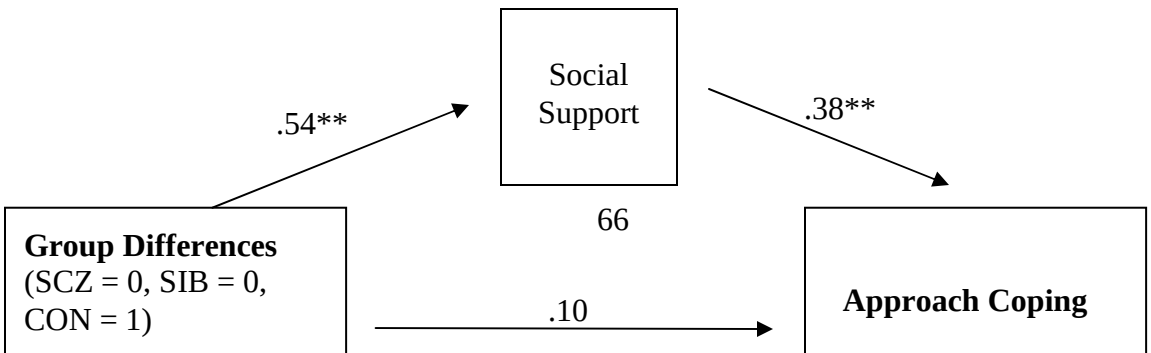

*12. Group differences in coping styles will be mediated by coping resources (cognitive ability and social support). That is, more social support and better cognitive ability will be associated with more use of approach coping.*

In response to general life stress, CON were significantly more likely than SCZ and SIB to use more approach coping. Differences between CON and SCZ on use of

approach coping during experimental stressors were not significant, therefore mediation was only tested for approach coping used in response to general life stress. As reported above, group differences in social support and cognitive ability were also significant.

As noted above, general approach coping was significantly positively correlated with social support but not cognitive ability. Therefore only social support was tested for mediation. As described above, CON were significantly different from both SCZ and SIB in their use of approach coping, but SIB and SCZ did not significantly differ from each other. Thus, the dummy coded variable comparing CON to both SIB and SCZ combined was used in place of the group variable. This dummy code was entered as the independent variable, approach coping to general life stress was entered as the dependent variable, and social support as the mediator. The first regression equation was used to regress the effect of approach coping (DV) on group (IV), $\beta = .30$, $t(95) = 3.09$, $p < .01$. Next, the mediator, social support was regressed on group, $\beta = .54$, $t(95) = 6.29$, $p < .01$. Then, the effect of social support was regressed on approach coping, while controlling for group. In this step, the beta weight for social support remained significant, $\beta = .38$, $t(95) = 3.39$, $p < .01$, but the beta weight for group was found to be nonsignificant, $\beta = .10$, $t(95) = .89$, $p > .05$. The total mediated effect was 4.56 (95% CI = 2.21 to 6.91). The sobel test ($z = 2.97$) confirmed that social support fully mediated group differences in approach coping ($p < .01$). See Figure 11.

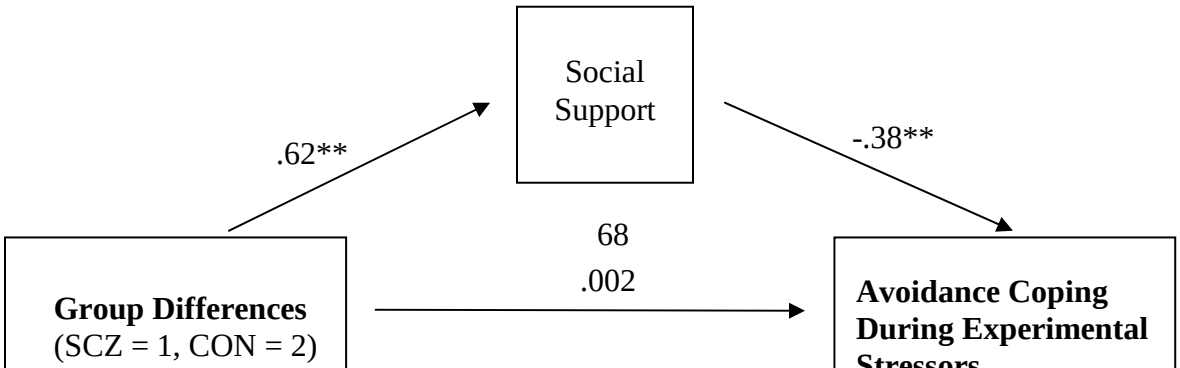
Figure 11. Mediation of group differences in approach coping by social support



As stated above, use of avoidance coping during general life stress was not related to either cognitive ability or social support and thus was not tested for mediation. Since there was a significant group difference in the use of avoidance coping strategies during experimental stressors between CON and SCZ, the composite measure for avoidance coping during experimental stressors described above was used to test whether group differences in use of avoidance coping were mediated by coping resources such as cognitive ability and social support. There was a significant negative correlation between avoidance coping to experimental stressors and cognitive ability, $r(78) = -.23$, $p < .05$, as well as between avoidance coping to experimental stressors and social support, $r(78) = -.40$, $p < .01$. These two mediator variables were entered into a series of regression equations to test for mediation. Group was entered as the independent variable, avoidance coping to experimental stressors was entered as the dependent variable, and cognitive ability and social support were entered as mediators. The first regression equation was used to regress the effect of avoidance coping during experimental stressors (DV) on group (IV), $\beta = -.27$, $t(78) = -2.46$, $p < .05$. Next, avoidance coping to experimental stressors (DV) was regressed on group (IV), $\beta = .002$, $t(78) = .01$, $p > .05$, as well as the two mediators: cognitive ability, $\beta = -.06$, $t(78) = -.53$, $p > .05$, and social support, $\beta = -.38$, $t(78) = -2.78$, $p < .01$. In the next set of equations, each mediator was independently

regressed on avoidance coping during experimental stressors (cognitive ability: β = .53, *t*(78) = 5.50, *p* < .01; social support: β = .62, *t*(78) = 7.03, *p* < .01). Using formulas described in MacKinnon (2008), the global and specific mediated effects were computed for these variables. In this model, there was a significant global mediated effect equal to -.48 (95% CI = -.82 to -.15). The specific mediated effect was significant for social support = 4.74 (95% CI = 1.64 to 7.84), but not for cognitive ability = -.66 (95% CI = -2.85 to 1.53). When social support and cognitive ability were in the model, group no longer significantly predicted avoidance coping to experimental stressors, β = .002, *t*(78) = .01, *p* > .05. Thus, there was full mediation of the effect of group (SCZ vs. CON) on use of avoidance coping during experimental stressors and this effect was primarily driven by social support, such that more social support was associated with less reliance of avoidance coping strategies. See Figure 12.

Figure 12. Multiple mediator model of group differences in use of avoidance coping during experimental stressors



In summary, mediation analyses revealed that social support fully mediated group differences in use of approach coping as well as group differences in perceived stress. Group differences in use of avoidance coping strategies during experimental stressors were also fully mediated by social support. Trend level group differences in perceived stress during role plays were fully mediated by threat appraisals during role plays.

## Chapter 6: Discussion

This study sought to elucidate factors that impact the experience of stress in individuals with schizophrenia and genetically high-risk siblings of individuals with schizophrenia by examining life events, stress associated specifically with those events, general perceived stress, subjective appraisals of stressful events, coping strategies, and coping resources such as cognitive ability and social support. In order to understand the relationships between psychological and physiological reactions to stress, all participants engaged in two laboratory tasks designed to engage the HPA axis and elicit a cortisol response. Results are discussed below.

### *Life Events, Perceived Stress and Coping Strategies*

As hypothesized, SCZ did not report more life events in the past year or more daily events in the past week compared to CON. These findings are consistent with previous reports that individuals with schizophrenia do not necessarily differ in the number of life events compared to normal populations (Walker et al., 2008). In order to address some of the shortcomings of other retrospective studies on life events (Phillips et al., 2007), mainly accounting for the desirability and personal impact of the event, the life events scale used in this study was modified to allow each participant to rate whether his/her experience of the event was good or bad and how stressful he/she found the event to be at the time of its occurrence. This allowed for the investigation of individual differences related to an event. For example, the event *separation from spouse or partner* may for some be a bad experience as it signals loss of a close relationship and source of social support. However, it is conceivable that some individuals might rate this item as good if it meant the end of an abusive relationship. There were no significant group differences in the number of events rated as good or bad within the past year, providing further support to the notion that individuals with SCZ do not experience bad events more frequently than CON. SIB did not differ significantly from SCZ or CON in the number of life events or the subjective stress associated with those events. This supports previous findings from the Edinburgh High-Risk Project, which also reported no differences in the number of life events experienced by a genetic high-risk group compared to healthy controls or first episode psychosis patients (Miller et al., 2001). This is the first study to specifically investigate individual differences in the subjective stress associated with life

events. Based on the current study, there is no evidence that individuals with SCZ or their high-risk siblings find life events to be more stressful than CON.

Given that day-to-day occurrences might be more meaningful in predicting health outcomes (Norman & Malla, 1994), daily events in the past week were also assessed. This questionnaire was similarly formatted to the life events scale described above. SCZ reported significantly fewer events in the past week than CON but they did not differ in the proportion of events they endorsed as good. There were no significant group differences in the average stress rating associated with weekly events. SIB also did not differ significantly from the two groups in the number of minor events in the past week, proportion of events endorsed as good, or stress associated with those events. Despite no group differences in these measures, on a global measure of perceived stress (perceived stress scale), SCZ reported significantly higher perceived stress than CON. SIB ratings for perceived stress were intermediate between SCZ and CON, although this difference was not statistically significant. Although total stress ratings on the weekly events questionnaire and perceived stress on the perceived stress scale were positively correlated, it appears that the perceived stress scale was able to capture some variance in the experience of stress in daily life not accounted for by the amount of stress that can be attributed to occurrence of specific events. It is possible that the cumulative effect of experiencing multiple stressors is greater than the sum of stress associated with individual stressors. This cumulative effect may have a differential impact on the experience of stress in different groups. Although not significant, SIB's score on the perceived stress scale was intermediate to SCZ and CON, providing support for the notion that an increase in the global experience of stress may be related to a genetic vulnerability

towards schizophrenia. Another possibility is that the experience of major or minor events differentially impacts mood in those with schizophrenia and those at high risk for schizophrenia compared to healthy controls. Mood associated with the occurrence of these events was not measured in this study. However, in an experience sampling study, Myin-Germeys and colleagues (2001) reported that compared to controls, individuals with schizophrenia and their high-risk relatives reported more decreases in positive affect and more increases in negative affect in response to daily events rated as stressful. Thus the differential impact of daily events in these populations may be better captured in mood associated with those events rather than in stress associated with those events. Although not assessed in the experience sampling study, the authors of the study noted that differences in stress appraisal and coping might mediate the effects of stress in individuals with schizophrenia and their high-risk relatives. It has also been suggested that differences in stress reactivity may be associated with different environmental and social circumstances such as reduced social support (Phillips et al., 2007).

In the current study, general coping strategies, social support and cognitive abilities were assessed to explore their relationships with perceived stress. Consistent with previous reports (Horan et al., 2007; Hultman et al., 1997; Jansen et al., 1999; Jansen et al., 2000b; Ventura et al., 2004), SCZ reported engaging in more avoidant coping strategies and less approach coping strategies than CON. SIB's use of avoidance coping strategies did not differ significantly from CON but they were significantly less likely than CON to use approach coping strategies. This finding suggests that the preference for SCZ to engage in more passive and avoidant coping strategies and less approach coping documented in previous studies is not entirely due to the disease process

as it is also seen in currently asymptomatic siblings of individuals with SCZ. The tendency for SIB to engage in less approach-related coping strategies may be indicative of the genetic liability towards schizophrenia. This liability might be expressed as a systematic alteration in the way one interacts with the environment. In other words, those at genetic high risk for developing schizophrenia are less likely to engage in approach coping strategies when faced with stressful events, which in turn might impact their perception of stress associated with those events.

Approach coping strategies include actively seeking emotional or instrumental support and guidance, thinking logically about the stressor and its effects, and using problem solving skills. More frequent use of these strategies is typically associated with better outcomes (Moos & Holahan, 2003). In a study of individuals with schizophrenia, Ventura and colleagues (2004) reported that certain personal characteristics, especially low self-efficacy, was associated with less use of approach coping strategies. In their study, the definition of self-efficacy included the perception of support and acceptance of family and friends. In the current study, this maps on to the measure of social support. As discussed below, both SCZ and SIB reported less perceived social support than CON and this might be one explanation for why these individuals are less likely to engage in approach coping. However, it is not clear from prior research what this relationship between approach coping and social support reflects. It could be that social support is needed to encourage individuals to engage the various strategies thought to comprise approach coping behavior. Alternatively, it could be that such coping strategies are learned or modeled through social relationships. If so, lack of appropriate social support may reduce opportunities to learn how to use potentially beneficial strategies.

In the current study, SCZ reported significantly less social support than CON, which is consistent with previous findings (Cohen & Sokolovsky, 1978; Hammer, 1981; Patterson et al., 1997). Also consistent with published reports (Heinrichs & Zakzanis, 1998), SCZ performed more poorly on cognitive tasks. SIB were intermediate between CON and SCZ on both of these variables. Perceived stress was significantly negatively correlated with approach coping. Perceived stress was also negatively correlated with social support and cognitive ability. However, when these variables were put in an informal multiple mediation model, only social support remained as a significant mediator of the group difference in perceived stress. Moreover, the mediation of perceived stress by social support was complete, indicating that group differences in perceived stress are fully explained by group differences in social support, not by group differences in cognitive ability or approach coping. Group differences in use of approach coping were also fully mediated by social support.

This finding highlights the role of social support in the day-to-day experiences of individuals with schizophrenia. As noted above, previous research speculated that differences in stress sensitivity may be explained by differences in coping strategies. The current study suggests that individuals with schizophrenia are more sensitive to environmental stress due to lower levels of social support. Level of social support has previously been shown to be negatively correlated with increased emotional reactivity towards daily stressors in other populations (Affleck et al., 1994; DeLongis et al., 1988). In this study, social support trumped cognitive ability as a significant mediator in explaining group differences in perceived stress. One of the most debilitating aspects of schizophrenia is a breakdown of interpersonal relationships, a major source of social

support. Many individuals with schizophrenia become socially withdrawn and isolated. It is unclear whether this withdrawal is associated with avolition (ambivalence or lack of will) or used as a strategy to deal with the other symptoms of schizophrenia like hallucinations or delusions (Walker et al., 1993). Yet research in the general population has found that social support can "act as a source of assistance" in coping with stress (Yanos & Moos, 2007). Thus it is possible that, since individuals with schizophrenia are especially at risk for low social support, it is this variable that is especially important (at least as compared to cognitive ability) in shaping day-to-day experiences in this population.

If, as theorized, the perception or the experience of stress does influence onset or relapse of psychosis (Phillips et al., 2007; Walker et al., 2008), one point of intervention could be increasing social support. Research on family intervention therapy in schizophrenia, a therapy in which one focus is to enhance support from family towards individuals with schizophrenia, has consistently reported reductions in relapse and in the number and duration of hospitalizations [see (Patterson & Leeuwenkamp, 2008) for a review]. Data from the current study point to the importance of social support in explaining individual differences in perceived stress, over and above any relationship between perceived stress and coping strategies or cognitive abilities. One caveat, however, is that this study measured *perceived* social support, which may or may not be an accurate measure of the actual amount of social support available to these individuals. On the one hand, the relationship between perception of social support and stress might be more meaningful since it taps directly into the resources that the individuals themselves have access to regardless of the objective availability of these resources.

However, it is important to keep in mind that there might be fundamental differences in what someone might constitute as a *normal* amount of social support. For example, there might be individual differences regarding preferences for a small or large social network. Some individuals might actually have adequate social support resources but are reluctant to use them (Buchanan, 1995). Social skills or social competence have been shown to be related to social networks (Burgha et al., 1993). Although, even though individuals with greater social skills have larger social networks, they do not necessarily perceive greater supports from these networks (Macdonald et al., 1998a). Thus, any treatment model incorporating social support must take these individual differences into account, focusing not only on how to increase social support for individuals with schizophrenia but also teaching these individuals how to appropriately assess and use these resources.

***Appraisal and Coping Responses to Experimental Stressors***

The two experimental stressors were picked based on a meta-analysis citing the utility of using a cognitive task in conjunction with a public-speaking task in eliciting an HPA response. The role plays were substituted for the public-speaking task because it was believed that engaging in a social interaction might be more generalizable to the types of stressors individuals with schizophrenia experience in daily life. Although SCZ reported more subjective stress associated with the experimental stressors than CON, the difference did not reach statistical significance (but approached trend levels for the role play tasks). Anecdotal evidence (i.e., speaking with participants after the experiment) suggests that perhaps SCZ did not fully engage in the PASAT and therefore did not find it stressful. This observation is supported by cortisol data which show an increase for CON between timepoints +20 and +30 (estimated to show the cortisol response to the

PASAT) but not for SCZ. It is possible that the PASAT was too difficult of a task for SCZ and they therefore did not engage in it to the same extent as CON. It is also possible that the role plays were more meaningful and engaging than the PASAT (i.e., having to interact with a neighbor or a landlord was more personally relevant than adding numbers) and therefore more stressful for SCZ, since they are known to have deficits in social functioning.

Although group differences in perceived stress associated with role plays were not significant, data support the notion that any trends towards group differences in subjective stress associated with role plays were fully mediated by threat appraisals. Use of avoidance coping during role plays was positively correlated with role play stress; however, when in the model with threat appraisals, use of avoidance coping was no longer a significant predictor of group differences in stress associated with engaging in role plays. Threat appraisal during role plays was also positively correlated with avoidance coping but unrelated to approach coping, suggesting that maladaptive cognitive appraisals are related to maladaptive coping strategies. As discussed above, social support was the only significant predictor for group differences in perceived stress related to weekly events. The current study did not measure appraisals for these events. Data from the experimental portion of the study suggests that threat appraisals may also be important in mediating group differences in perceived stress. Theoretically, one's appraisal of an event is in part related to one's coping resources. If one does not perceive to have adequate resources for coping with the demands of the situation, that situation is more likely to be appraised as a threat. In individuals with schizophrenia, who are known to have diminished social support, it would be interesting to test whether stress related to

daily encounters is mediated by a global perception of threat (presumably related in part to their lack of social support) or whether social support alone stands out as the more meaningful variable in understanding their experiences of stress.

***Cortisol Response to Experimental Stressors***

Although the contemporary theories linking stress, HPA dysfunction, and schizophrenia posit that individuals with schizophrenia are hypersensitive to stress, resulting in higher levels of circulating cortisol, which in turn is related to higher levels of dopamine [see (Walker et al., 2008) for a review], data from the current investigation show that individuals with SCZ and those at genetic high risk for schizophrenia show *less* cortisol reactivity to a specific stressor than CON. Although the differences were not statistically significant, this pattern of cortisol hyporesponsivity was evident among SCZ and SIB despite their verbal reports that they found the PASAT and the role plays to be *more* stressful than CON. The effect size for these differences between SCZ vs. CON and SIB vs. CON were small to medium in magnitude, suggesting that a study powered with a larger sample size might have yielded significant results. Data from the current study generally support previous findings that individuals with schizophrenia show less HPA axis responsivity (as measured by cortisol output) in the face of psychosocial stress (Jansen et al., 1998; Jansen et al., 2000b). Albeit of a small effect size, the same pattern of HPA hyporesposivity was also observed in genetic high-risk, asymptomatic, unmedicated siblings of individuals with schizophrenia, suggesting that this phenomenon is not entirely due to medication effects.

It has been postulated that individuals with schizophrenia show less HPA activity in response to psychosocial stressors because they may not be able to respond to these

types of stressors or have difficulty interpreting its contexts (Gispen-de Wied & Jansen, 2002). It is also possible that despite feeling psychologically stressed, their bodies are not able to adequately process the stress and mobilize the resources to mitigate the stressor. According to McEwen (2000), disease susceptibility is enhanced when the stress response systems do not adequately respond to their environment. In the short-term, HPA axis hormones released in response to stress are believed to ensure the maintenance of homeostasis through activation and coordination of various psychological and physiological processes, such as memory consolidation, immune functioning, cardiovascular activation, glucose metabolism, and emotional processing (Sapolsky et al., 2000; Schulkin et al., 1994). Part of the vulnerability to schizophrenia may be an inability to properly respond to psychosocial stressors, which may in itself become a state of heightened stress, leading to higher levels of baseline cortisol.

Previous research on first degree relatives of individuals with schizophrenia has shown that increased risk for psychosis is associated with increased emotional reactivity to the small stresses in life (Myin-Germeys & van Os, 2007). There have been no studies that have specifically investigated the subjective experience of stress with the biological stress response in individuals with schizophrenia and their high-risk siblings. Data from the current study show that the psychological response to a stressor is not correlated with the response of the HPA system (i.e., no correlation between subjective reports of stress of experimental stressors and cortisol reactivity). Thus, these data suggest that increased emotional reactivity to small stresses in life may not be coupled with increased physiological reactivity per se.

Previous research shows that a blunting of the cortisol response in schizophrenia is specific to psychosocial stressors and not physical stressors (Jansen et al., 2000b). For example, injection of a synthetic glucocorticoid should theoretically cause an inhibition of cortisol secretion through a negative feedback loop. However in individuals with schizophrenia, this procedure, known as the dexamethosone suppression test, produces the opposite effect. That is, individuals with schizophrenia show a failure to suppress cortisol release, providing evidence of an impaired negative feedback mechanism in this population. This finding is paradoxical to the reports of cortisol hyporesponsivity to psychosocial stress. One possible explanation is that physical and psychological stressors engage the HPA axis via different pathways. There is some evidence that physical stimuli appear to elicit HPA responses with corticotrophin releasing hormone (CRH), while psychological stimuli appear to elicit HPA responses mostly via arginin-vasopressin (AVP) (Romero & Sapolsky, 1996). In individuals with schizophrenia, the diminished cortisol response to the psychosocial stressor may be caused by disturbances in the pathways responsible for the stimulation of the HPA system via AVP (Jansen et al., 2000b). Future investigations on HPA responsivity to psychosocial stressors should account for the complexities of the system and target their investigations specifically towards the pathway through which psychosocial stress might influence the biologic stress response system.

The notion that use of passive and avoidant coping strategies by individuals with schizophrenia may contribute to their impaired stress response (Jansen et al., 2000b) was not supported by this study. Cortisol reactivity was not related to use of approach or avoidant coping strategies during experimental stressors. HPA reactivity does however

appear to be related to challenge appraisals, such that higher challenge appraisals are related to higher cortisol reactivity. Since SCZ were less likely than CON to make challenge appraisals, it is possible that the HPA hyporesponsivity seen in SCZ may in part be due to lack of challenge appraisals, which may be part of the appropriate stress response. For example, appraising stressors as challenges is related to increased cortisol responsivity because both mechanisms might foster behaviors aimed at successfully mitigating the effects of stress.

In summary, the study provides evidence that although individuals with schizophrenia and their high-risk siblings do not necessarily differ in the number of major or minor life events, they report leading more stressful lives in general. These group differences in perceived stress are fully mediated by perceived social support, over and above any differences in use of approach related coping strategies or cognitive ability. Although not significant, the finding that SIB's report of perceived stress was intermediate to that of CON and SCZ suggests that increases in the perception of stress is not solely related to the schizophrenia disease process. In fact, it highlights the potential role of the genetic vulnerability towards developing schizophrenia in the global perception of stress. It is possible that a genetic vulnerability towards schizophrenia sensitizes one to the social environment and makes it appear more stressful. This perception of stress seems to be mediated by social support.

This study also adds to the small literature on cortisol hyporesponsivity to psychosocial stress in individuals with schizophrenia. SIB showed a similar pattern of cortisol hyporesponsivity, again suggesting that the impaired HPA response previously observed in individuals with schizophrenia cannot solely be due to the disease process or

medication effects and may be related to the genetic vulnerability towards developing schizophrenia. The HPA response to experimental stressors was not associated with participants' subjective reports of how stressful the task was, suggesting at least a partial dissociation between the biological and psychological stress processing mechanisms.

***Strengths and Limitations***

The strengths of the current study include the comprehensive nature of the measure of stress (life events, weekly events, perceived stress) and its psychological (appraisal, coping) and biological (cortisol) sequelae. This is the first study to examine the appraisal and coping processes associated with laboratory induced psychosocial stressors in conjunction with a measure of the HPA axis response in schizophrenia and individuals at high-risk for schizophrenia. Results have implications for treatment in schizophrenia, especially as they relate to social support reducing the impact of day-to-day stressors in individuals with schizophrenia. Results also have implications for genetic high-risk individuals, who may be at risk for lower social support because of higher levels of inherited schizoid-like traits.

One major limitation of the current study is that results may not be specific to schizophrenia. The diathesis-stress model provides a framework for understanding many psychiatric illnesses (Depression, PTSD, etc). It is possible that an increased sensitivity to stress and / or abnormal stress reactivity is present in all vulnerable populations and the genetic diathesis may ultimately determine specific psychiatric outcome. Another major limitation is the small sample size for SIB. Although they were intermediate between CON and SCZ on many variables of interest, the differences did not reach statistical significance. Therefore, it is difficult to draw strong conclusions based on these data.

The study is also confounded by the effect of medications. Most of the SCZ sample was on antipsychotic medications. A medication-free sample was specifically not recruited to enhance the generalizability of results to the majority of individuals with schizophrenia, for whom an antipsychotic medication regimen in part of their treatment. Although it is informative to observe the effects of psychosocial stress in individuals in as "natural" a state as possible, the effect of antipsychotic medication on the stress response cannot be discounted. It is well known that part of the therapeutic effect of antipsychotic medications is to dampen HPA reactivity and reduce sensitivity to stress (Meier et al., 2005). Nonetheless, the same pattern of cortisol hyporesponsivity was also observed in SIB, none of whom were taking antipsychotic medications. Thus, the reduced cortisol reactivity seen in SCZ could not entirely be due to medications.

***Future Directions***

Future studies on stress reactivity in schizophrenia should focus on the differential effects of physical and psychosocial stressors on the HPA axis. It will be informative to include measures of cognitive appraisal and coping in these studies. For example, will threat appraisals mediate differences in perceived stress related to physical stressors? It will also be informative to investigate individual differences in cognitive appraisals. For example, why do individuals with schizophrenia appraise events as more threatening? If threat appraisals are related, in part, to coping resources such as social support, does increasing social support change one's patterns of cognitive appraisals? Future studies should also focus on how to increase the perception of social support in individuals with schizophrenia. As discussed above, this study only examined each individual's perception of social support, which may or may not be related to objective measures of social

support. Although the ISEL is moderately well correlated with objective measures of social support, like number of friends, it is not clear whether in individuals with schizophrenia objective and perceived social support are as tightly coupled as in the healthy population. Therefore, in this population simply increasing availability of social support may not change the *perception* of social support because of the prominence of symptoms such as anhedonia and avolition. Ultimately, finding better interventions for these negative symptoms might be necessary to mitigate the effects of daily stress in this population.

Individuals at genetic high-risk for schizophrenia remain an interesting and informative group to study. They have the potential to provide information on the genetic vulnerability towards schizophrenia without confounding results with byproducts of the disease process or with medications. There is a dearth of literature on stress reactivity among these high-risk individuals. The current study provides a basis for further investigating cortisol reactivity to psychosocial stress in this group. They show a hypoactive response to stress that was intermediate to that of CON and SCZ, which warrants further study as it has the potential to inform us about the genetic vulnerability towards abnormal stress processing. Longitudinal investigations on the development of the HPA axis also have the potential to inform us about the timing and circumstances under which the HPA axis becomes functionally abnormal.

Thus far, there is a debate in the literature about providing treatment to high-risk individuals since current knowledge on prediction about conversion to psychosis lacks sensitivity. Further research on the role of social support as a protective factor in a vulnerable population can guide behavioral interventions to delay the progression of

psychosis. It would also be informative to study high-risk siblings of other psychiatric patients to determine the specificity of the vulnerability towards abnormal stress processes. Such research has the potential to inform primary prevention efforts in high-risk populations.

Experience sampling studies provide a unique way to assess the impact of stressors in the natural environment. Laboratory induced stressors may not engage the participant enough to invoke a true stress response. Information about how individuals with schizophrenia as well as high-risk individuals assess and cope with the stressors they encounter in daily life can be more useful in understanding the stress processing mechanisms in this population.

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